Answer 1:

Bibliographic Information

Efficacy of three potent steroid sulfatase inhibitors: pre-clinical investigations for their use in the treatment of hormone-dependent breast cancer. Foster, Paul A.; Chander, Surinder K.; Parsons, Michael F. C.; Newman, Simon P.; Woo, L. W. Lawrence; Potter, Barry V. L.; Reed, Michael J.; Purohit, Atul. Department of Endocrinology and Metabolic Medicine and Sterix Ltd, Imperial College Faculty of Medicine, St Mary's Hospital, London, Breast Cancer Research and Treatment (2008), 111(1), 129-138. Publisher: Springer, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. AN 2008:861430 CAPLUS

Abstract

Estrogenic steroids, such as estradiol, are known to play a crucial role in the development and growth of hormone-dependent breast cancer. Steroid sulfatase (STS) inhibitors that can prevent the biosynthesis of these steroids via the sulfatase pathway offer therapeutic potential. We show here the in vivo profile, including the efficacy in a xenograft breast cancer model and pharmacokinetics, of three potent STS inhibitors. MCF-7 cells stably over-expressing STS cDNA (MCF-7STS) were generated. Ovariectomized, MF-1, female nude mice receiving s.c. injections of estradiol sulfate (E2S) and bearing MCF-7STS xenografts, were orally treated with the STS inhibitors STX64, STX213, and STX1938. Treatment was administered once weekly at a dose of 1 mg/kg for 35 days during which animals received E2S thrice weekly. Mice were weighed and tumor measurements taken weekly. Furthermore, the pharmacokinetics for STX213 was detd. in rats. STX213 and STX1938 exhibited potent STS inhibition in vivo. However, STX1938 demonstrated a greater duration of activity. In vehicle treated nude mice receiving E2S, tumor vols. increased by 260% after 35 days compared to day zero. STX64 (1 mg/kg) failed to reduce tumor growth when given once weekly. STX213 and STX1938 (once weekly, 1 mg/kg) significantly inhibited ($P < 0.05$) tumor growth over this same time period. These compds. completely inhibited liver and tumor STS activity and significantly reduced the levels of plasma E2. This study indicates that the STS inhibitor, STX213, exhibits excellent efficacy and pharmacokinetics and therefore offers a potentially novel treatment for hormone-dependent breast cancer.

Answer 2:

Bibliographic Information

Inhibition of Estradiol Receptor/Src Association and Cell Growth by an Estradiol Receptor α Tyrosine-Phosphorylated Peptide. Varricchio, Lilian; Migliaccio, Antimo; Castoria, Gabriella; Yamaguchi, Hiroshi; de Falco, Antonietta; Di Domenico, Marina; Giovannelli, Pia; Farrar, William; Appella, Ettore; Auricchio, Ferdinando. Dipartimento di Patologia Generale, II Universita di Napoli, Naples, Italy. Molecular Cancer Research (2007), 5(11), 1213-1221. Publisher: American Association for Cancer Research, CODEN: MCROC5 ISSN: 1541-7786. Journal written in English. CAN 148:113389 AN 2007:1319936 CAPLUS

Abstract

This report offers direct evidence that assocn. of the estradiol receptor (ER) with Src triggered by steroid agonists or growth factors controls breast and prostate cancer cell growth. This assocn. is abolished in whole cells and in vitro by a six-amino-acid peptide that mimics the sequence around the phosphotyrosine residue in position 537 of the human ERα. The phosphorylated peptide, at nanomolar concns., is taken up by MCF-7 and LNCaP cells derived from human mammary and prostate cancers, resp. In addn., to block the ER/Src interaction, the phosphopeptide inhibits Src/Erk pathway, cyclin D1 expression, and DNA synthesis induced by estradiol or androgen or triggered by epidermal growth factor. In contrast, no inhibition of the Src-mediated epidermal growth factor action on DNA synthesis is detectable in human mammary cancer cells that do not express ER (MDA-MB231), indicating that the peptide specifically targets the ER-assocd. Src. Remarkably, the peptide, in contrast with classic steroid antagonists, does not interfere in ER- or androgen receptor-dependent transcriptional activity. Nevertheless, it markedly inhibits the growth of MCF-7 cell xenografts induced in immunodepressed and estradiol-treated mice. The present report suggests that inhibition of assocn. of steroid receptors with Src or other signaling effectors may have therapeutic applications for patients with ER-pos. tumors.

Answer 3:

Bibliographic Information

In vivo resolution of multiexponential decays of multiple near-infrared molecular probes by fluorescence lifetime-gated whole-body time-resolved diffuse optical imaging. Akers, Walter; Lesage, Frederic; Holten, Dewey; Achilefu, Samuel. Optical Radiology Lab, Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA. Molecular Imaging (2007), 6(4), 237-246. Publisher: BC Decker Inc., CODEN: MIOMBP ISSN: 1535-3508. Journal written in English. CAN 148:73167 AN 2007:1176882 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The biodistribution of two near-IR fluorescent agents was assessed in vivo by time-resolved diffuse optical imaging. Bacteriochlorophyll a (BC) and cypate-glysine-arginine-aspartic acid-serine-proline-lysine-OH (Cyp-GRD) were administered sep. or combined to mice with s.c. xenografts of human breast adenocarcinoma and slow-release estradiol pellets for improved tumor growth. The same excitation (780 nm) and emission (830 nm) wavelengths were used to image the distinct fluorescence lifetime distribution of the fluorescent mol. probes in the mouse cancer model. Fluorescence intensity and lifetime maps were reconstructed after raster-scanning whole-body regions of interest by time-correlated single-photon counting. Each captured temporal point-spread function (TPSF) was deconvolved using both a single and a multiexponental decay model to best det. the measured fluorescence lifetimes. The relative signal from each fluorophore was estd. for any region of interest included in the scanned area. Deconvolution of the individual TPSFs from whole-body fluorescence intensity scans provided corresponding lifetime images for comparing individual component biodistribution. In vivo fluorescence lifetimes were detd. to be 0.8 ns (Cyp-GRD) and 2 ns (BC). This study demonstrates that the relative biodistribution of individual fluorophores with similar spectral characteristics can be compartmentalized by using the time-domain fluorescence lifetime gating method.

Answer 4:

Bibliographic Information

Effects of a phytoestrogen-containing soy extract on the growth-inhibitory activity of ICI 182 780 in an experimental model of estrogen-dependent breast cancer. Gallo, Daniela; Mantuano, Elisabetta; Fabrizi, Manuela; Ferlini, Cristiano; Mozzetti, Simona; De Stefano, Ilaria; Scambia, Giovanni. Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Rome, Italy. Endocrine-Related Cancer (2007), 14(2), 317-324. Publisher: Society for Endocrinology, CODEN: ERCAE9 ISSN: 1351-0088. Journal written in English. CAN 147:514581 AN 2007:1096028 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The study reported here was designed to det. whether a phytoestrogen-contg. soy ext. (SSE) could negate/overwhelm the inhibitory effects of ICI 182 780 on the growth of estrogen-sustained human breast cancer xenografts (MCF-7), in ovariectomized athymic mice. As expected, estradiol-supplemented tumors did not grow over the study period in ICI 182 780-treated females; concomitant administration of 50 mg/kg per day SSE slightly potentiated the inhibitory activity of the drug, while at 100 mg/kg per day, SSE partially negated ICI 182 780 activity. In keeping with these in vivo outcomes, we obsd. that the level of cyclin D1 (and progesterone receptor) in MCF-7 xenografts was considerably reduced by ICI 182 780, an effect enhanced by concomitant treatment with 50 SSE, but reduced by the higher dosage (i.e. 100 mg/kg per day). Thrombospondin-1 (TSP-1) and kallikrein 6 (KLK6) levels were also reduced following ICI 182 780, although to a lesser degree; again, combined anti-estrogen and SSE produced a dose-dependent regulation in TSP-1 and KLK6 tumor level, with a further redn. in the mRNA gene expression at 50 SSE (compared with ICI 182 780) and a partial reversion of the drug-induced down-regulation at 100 mg/kg per day. No modulation was detected in the serum concn. of IGF-1 (a potent mitogen for estrogen receptor-pos. breast cancer cell lines) either upon treatment with ICI 182 780 or concomitant administration of the anti-estrogen with SSE. In conclusion, results from this study raise concerns about the consumption of isoflavone supplements in conjunction with ICI 182 780 therapy, in postmenopausal women with estrogen-dependent breast cancer.

Answer 5:

Bibliographic Information

An α-fetoprotein-derived peptide reduces the uterine hyperplasia and increases the antitumor effect of tamoxifen.
Andersen, T. T.; Georgekutty, J.; DeFreest, L. A.; Amaratunga, G.; Narendran, A.; Lemanski, N.; Jacobson, H. I.; Bennett, J. A. Center for Cardiovascular Sciences, Albany Medical College, Albany, NY, USA. British Journal of Cancer (2007), 97(3), 327-333. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 149:143292 AN 2007:830349 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Tamoxifen (Tam) is effective for the treatment and prevention of breast cancer. However, it has toxic drawbacks and has limited-duration utility because, over time, human tumors become refractory to Tam. Recently, a new nontoxic peptide, α-fetoprotein-derived peptide (AFPep) has been proposed for the treatment and prevention of breast cancer. The purpose of this paper is to det. whether combining AFPep with Tam would increase efficacy and reduce toxicity in exptl. models of breast cancer. Low doses of AFPep and Tam were more effective in combination than either agent alone against breast cancer growth in cell culture, in tumor-xenografted mice, and in carcinogen-exposed rats. α-Fetoprotein-derived peptide interfered with Tam-induced uterine hyperplasia in immature mice, and showed no toxic effects. Unlike Tam, AFPep did not inhibit binding of estradiol (E2) to estrogen receptor (ER). Thus, these two agents utilize different mechanisms to interfere with ER functionality, yet work cooperatively to reduce breast cancer growth and alleviate Tam's troubling toxicity of uterine hyperplasia and appear to be a rational combination for the treatment of ER-pos. breast cancer.

Answer 6:

Bibliographic Information

β-2-Microglobulin Is an Androgen-Regulated Secreted Protein Elevated in Serum of Patients with Advanced Prostate Cancer.
Gross, Mitchell; Top, Irina; Laux, Isett; Katz, Jonathan; Curran, John; Tindell, Charles; Agus, David. Louis Warschaw Prostate Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA. Clinical Cancer Research (2007), 13(7), 1979-1986. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 148:6997 AN 2007:369838 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: A better understanding of secreted proteins may lead to the discovery of new biomarkers, which, along with prostate-specific antigen (PSA), may be useful in the diagnosis and treatment of prostate cancer patients. Exptl. DESIGN: Conditioned medium was collected from LNCaP cells following stimulation with methyltrienolone (R1881), 17β-estradiol (estradiol), or interleukin-6 and analyzed for differential protein expression with surface-enhanced laser desorption/ionization-time of flight mass spectrometry. Quant. reverse transcription-PCR, immunoblots, and ELISA were used to measure β-2-microglobulin (B2M) message and protein levels in cells, conditioned medium, and serum. RESULTS: Surface-enhanced laser desorption/ionization-time of flight revealed that many peaks were induced or repressed following stimulation with R1881 or estradiol. A peak of interest centered at 11.8 kDa was chosen for addnl. anal. Immunodepletion identified the peak of interest as B2M. Reverse transcription-PCR and immunoblots confirmed that PSA and B2M were induced by R1881. However, unlike PSA, B2M was not increased on stimulation with estradiol or interleukin-6. Human B2M is identified in the serum of mice bearing human prostate cancer xenograft. B2M is expressed in human prostate cancer cell lines and tissues. Serum B2M levels are elevated in patients with metastatic, androgen-independent prostate cancer. CONCLUSIONS: B2M is a secreted protein expressed in prostate cancer, which is more specific for androgen stimulation than PSA under the conditions tested. Addnl. studies are warranted to explore if B2M is as useful marker for prostate cancer. Identification of proteins secreted from cancer cells in preclin. models may be a useful strategy for biomarker discovery.

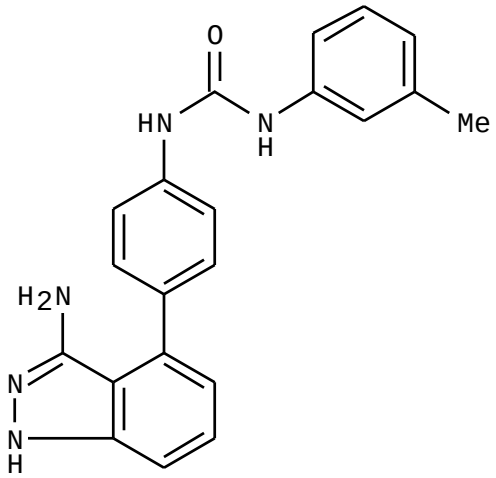
Answer 7:

Bibliographic Information

Discovery of N-(4-(3-Amino-1H-indazol-4-yl)phenyl)-N'-(2-fluoro-5-methylphenyl)urea (ABT-869), a 3-Aminoindazole-Based Orally Active Multitargeted Receptor Tyrosine Kinase Inhibitor. Dai, Yujia; Hartandi, Kresna; Ji, Zhiqin; Ahmed, Asma A.; Albert, Daniel H.; Bauch, Joy L.; Bouska, Jennifer J.; Bousquet, Peter F.; Cunha, George A.; Glaser, Keith B.; Harris, Christopher M.; Hickman, Dean; Guo, Jun; Li, Junling; Marcotte, Patrick A.; Marsh, Kennan C.; Moskey, Maria D.; Martin, Ruth L.; Olson, Amanda M.; Osterling, Donald J.; Pease, Lori J.; Soni, Niru B.; Stewart, Kent D.; Stoll, Vincent S.; Tapang, Paul; Reuter, David R.; Davidsen, Steven K.; Michaelides, Michael R. Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, IL, USA. Journal of Medicinal Chemistry (2007), 50(7), 1584-1597. Publisher: American Chemical Society, CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 146:474757 AN 2007:253150 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In our continued efforts to search for potent and novel receptor tyrosine kinase (RTK) inhibitors as potential anticancer agents, we discovered, through a structure-based design, that 3-aminoindazole could serve as an efficient hinge-binding template for kinase inhibitors. By incorporating an N,N'-diaryl urea moiety at the C4-position of 3-aminodazole, a series of RTK inhibitors were generated, which potently inhibited the tyrosine kinase activity of the vascular endothelial growth factor receptor and the platelet-derived growth factor receptor families. A no. of compds. with potent oral activity were identified by utilizing an estradiol-induced mouse uterine edema model and an HT1080 human fibrosarcoma xenograft tumor model. In particular, compd. 17p (ABT-869)(I) was found to possess favorable pharmacokinetic profiles across different species and display significant tumor growth inhibition in multiple preclin. animal models.



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Answer 8:

Bibliographic Information

Role for HER2/neu and HER3 in fulvestrant-resistant breast cancer. Osipo, Clodia; Meeke, Kathleen; Cheng, Dong; Weichel, Alyssa; Bertucci, Anne; Liu, Hong; Jordan, V. Craig. Department of Pathology, Oncology Institute, Cardinal Bernadin Cancer Center, Loyola University Medical Center, Maywood, IL, USA. International Journal of Oncology (2007), 30(2), 509-520. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 146:308719 AN 2007:198897 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Tamoxifen resistance is common for estrogen receptor α (ERα) pos. breast cancer. Second-line therapies include aromatase inhibitors or fulvestrant. We have shown previously that fulvestrant reversed 17β-estradiol-induced tumor regression of tamoxifen-stimulated MCF-7 xenografts (MCF-7TAMLT) treated for >5 years with tamoxifen in athymic mice and paradoxically stimulated growth. We investigated mechanisms responsible for growth by fulvestrant in the presence of physiol. estradiol and therapeutic strategies in vivo.

The results demonstrated that only estradiol increased expression of the estrogen-responsive genes, c-myc, igf-1, cathepsin D, and pS2 mRNAs, in MCF-7E2 and MCF-7TAMLT tumors. Tamoxifen or fulvestrant decreased the estradiol-induced increase of these mRNAs in both tumor models. However, tyrosine-phosphorylated HER2/ neu, HER3, phospho-extracellular-regulated kinase-1/2 (ERK-1/2), and phospho-glycogen synthetase kinase 3α (GSK3α) and β proteins were increased in MCF-7TAMLT tumors treated with fulvestrant compared to estradiol, control, or tamoxifen. Phospho-HER2/neu interacted with HER3 protein in MCF-7TAMLT tumors. In order to det. whether the functional interaction of HER2/neu with HER3 is crit. for growth of fulvestrant-stimulated MCF-7TAMLT tumors, pertuzumab (an antibody that blocks HER2/neu-HER3 interaction) was used in an in vivo xenograft growth assay. Only growth of fulvestrant-treated MCF-7TAMLT xenografts was decreased significantly by 37.2% in response to pertuzumab (P = 0.004). Pertuzumab specifically decreased the interaction of HER2/neu protein with HER3 in fulvestrant-stimulated MCF-7TAMLT tumors. These results suggested growth of MCF-7TAMLT tumors by tamoxifen or fulvestrant is potentially independent of ERα transcriptional activity as evidenced by lack of induction of four estrogen-responsive genes. The results suggested that growth of MCF-7TAMLT tumors treated with fulvestrant in the presence of physiol.
estradiol is in part mediated through enhanced signaling from the HER2/neu-HER3 pathway as pertuzumab partially inhibited growth and the interaction of HER2/neu with HER3 in vivo.

Answer 9:

Bibliographic Information

Inhibition of androgen-independent prostate cancer by estrogenic compounds is associated with increased expression of immune-related genes. Coleman, Iisa M.; Kiefer, Jeffrey A.; Brown, Lisha G.; Pitts, Tiffany E.; Nelson, Peter S.; Brubaker, Kristen D.; Vessella, Robert L.; Corey, Eva. Fred Hutchinson Cancer Research Center, Seattle, Seattle, WA, USA. Neoplasia (Ann Arbor, MI, United States) (2006), 8(10), 862-878. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. http://www.neoplasia.com/pdf/manuscript/neo06328.pdf Journal; Online Computer File written in English. CAN 146:93710 AN 2006:1213429 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The clin. utility of estrogens for treating prostate cancer (CaP) was established in the 1940s by Huggins. The classic model of the anti-CaP activity of estrogens postulates an indirect mechanism involving the suppression of androgen prodn. However, clin. and preclin. studies have shown that estrogens exert growth-inhibitory effects on CaP under low-androgen conditions, suggesting addnl. modes whereby estrogens affect CaP cells and/or the microenvironment. Here the authors have investigated the activity of 17β estradiol (E2) against androgen-independent CaP and identified mol. alterations in tumors exposed to E2. E2 treatment inhibited the growth of all four androgen-independent CaP xenografts studied (LuCaP 35V, LuCaP 23.1AI, LuCaP 49, and LuCaP 58) in castrated male mice. The mol. basis of growth suppression was studied by cDNA microarray anal., which indicated that multiple pathways are altered by E2 treatment. Of particular interest are changes in transcripts encoding proteins that mediate immune responses and regulate androgen receptor signaling. In conclusion, the authors' data show that estrogens have powerful inhibitory effects on CaP in vivo in androgen-depleted environments and suggest novel mechanisms of estrogen-mediated antitumor activity. These results indicate that incorporating estrogens into CaP treatment protocols could enhance therapeutic efficacy even in cases of advanced disease.

Answer 10:

Bibliographic Information

Estrogenic Regulation of Host Immunity against an Estrogen Receptor-Negative Human Breast Cancer. Curran, Edward M.; Judy, Barbara M.; Duru, Ngozi A.; Wang, Hui-Qun; Vergara, Leoncio A.; Lubahn, Dennis B.; Estes, D. Mark. Department of Pediatrics, Sealy Center for Vaccine Development, University of Texas Medical Branch at Galveston, Galveston, TX, USA. Clinical Cancer Research (2006), 12(19), 5641-5647. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:79027 AN 2006:1028740 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The risk of developing breast cancer is pos. correlated with exposure to increased levels of estrogen and/or an increased duration of estrogen exposure. Many different mechanisms have been proposed to explain the assocn. of estrogens with breast cancer risk; however, the well-documented immune modulatory properties of estrogen have received little attention. In part, this is due to a lack of suitable models for studying this relationship. Exptl. Design: We have developed an animal model using estrogen receptor (ER)-neg. human breast cancer cell line, MDA-MB-468, xenografted into severe combined immunodeficient (SCID) mice. We also generated the ER-α knockout (ER-αKO) mice on the SCID background and then tested the ability of 17{szligbeta}-estradiol to stimulate growth of xenografted ER-neg. human breast cancer tumors in wild-type and ER-αKO SCID mice. We quantified vascularization of tumors, macrophage recruitment to the tumor site by immunocytochem., and inflammatory cytokine prodn. RESULTS: We show that estrogen treatment of C57BL/6/SCID mice promotes the growth of xenografted ER-neg. tumors in wild-type mice and this estrogen-induced tumor growth is abrogated in ER-αKO mice. Tumor neovascularization of estrogen-treated mice was unchanged vs. control; however, estrogen treatment of the C57BL/6/SCID host suppressed macrophage recruitment to and inflammatory cytokine prodn. at the tumor site. CONCLUSIONS: These data are consistent with estrogen modulation of the inflammatory response as a contributing factor in estrogen-stimulated growth of an ER-neg. tumor. This effect on the host innate immune response was mediated by ER-α.

Answer 11:

Bibliographic Information

Genes regulated by estrogen in breast tumor cells in vitro are similarly regulated in vivo in tumor xenografts and human breast tumors. Creighton, Chad J.; Cordero, Kevin E.; Larios, Jose M.; Miller, Rebecca S.; Johnson, Michael D.; Chinnaiyan, Arul M.; Lippman, Marc E.; Rae, James M. Bioinformatics Program, University of Michigan Medical Center, Ann Arbor, MI, USA. GenomeBiology (2006), 7(4), No pp. given. Publisher: BioMed Central Ltd., CODEN: GNBLFW ISSN: 1465-6914. http://genomebiology.com/content/pdf/gb-2006-7-4-r28.pdf Journal; Online Computer File written in English. CAN 145:452533 AN 2006:503528 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Estrogen plays a central role in breast cancer pathogenesis. Although many studies have characterized the estrogen regulation of genes using in vitro cell culture models by global mRNA expression profiling, it is not clear whether these genes are similarly regulated in vivo or how they might be coordinately expressed in primary human tumors. Results: We generated DNA microarray-based gene expression profiles from three estrogen receptor α (ERα)-pos. breast cancer cell lines stimulated by 17β-estradiol (E2) in vitro over a time course, as well as from MCF-7 cells grown as xenografts in ovariectomized athymic nude mice with E2 supplementation and after its withdrawal. When the patterns of genes regulated by E2 in vitro were compared to those obtained from xenografts, we found a remarkable overlap (over 40%) of genes regulated by E2 in both contexts. These patterns were compared to those obtained from published clin. data sets. We show that, as a group, E2-regulated genes from our preclin. models were co-expressed with ERα in a panel of ERα+ breast tumor mRNA profiles, when corrections were made for patient age, as well as with progesterone receptor. Furthermore, the E2-regulated genes were significantly enriched for transcriptional targets of the myc oncogene and were found to be coordinately expressed with Myc in human tumors. Conclusion: Our results provide significant validation of a widely used in vitro model of estrogen signaling as being pathol. relevant to breast cancers in vivo.

Answer 12:

Bibliographic Information

Effects of gonadotrophin treatments on meiotic and developmental competence of oocytes in porcine primordial follicles following xenografting to nude mice. Kaneko, Hiroyuki; Kikuchi, Kazuhiro; Noguchi, Junko; Ozawa, Manabu; Ohnuma, Katsuhiko; Maedomari, Naoki; Kashiwazaki, Naomi. Genetic Diversity Department, National Institute of Agrobiological Sciences, Kannondai 2-1-2, Tsukuba, Ibaraki, Japan. Reproduction (Bristol, United Kingdom) (2006), 131(2), 279-288. Publisher: Bioscientifica Ltd., CODEN: RCUKBS ISSN: 1470-1626. Journal written in English. CAN 144:404534 AN 2006:252624 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors' objective was to improve the developmental ability of oocytes in porcine primordial follicles xenografted to nude mice, by treating the host mice with gonadotrophins to accelerate follicular growth. Ovarian tissues from 20-day-old piglets, in which most of the follicles were primordial, were transplanted under the kidney capsules of ovariectomized nude mice. Gonadotrophin treatments were commenced around 60 days after vaginal cornification in the mice. Ovarian grafts were obtained 2 or 3 days after treatment with equine chorionic gonadotropin (eCG-2 and eCG-3 groups), after porcine FSH infusion for 7 or 14 days, or after infusion of porcine FSH for 14 days with a single injection of estradiol antiserum (FSH-7, FSH-14 and FSH-14EA groups, resp.). Gonadotrophin treatments accelerated follicular growth within the xenografts compared with that in control mice given no gonadotrophins, consistent with higher ($P < 0.05$) circulating inhibin levels in the gonadotrophin-treated mice. In contrast, circulating mouse FSH levels were significantly ($P < 0.05$) depressed. The authors recovered large nos. of full-sized oocytes with meiotic competence to the mature stage from the eCG-3, FSH-7, and FSH-14EA, unlike in the control group. Moreover, 56% of matured oocytes with the first polar body (n = 39) were fertilized in vitro in the FSH-14EA group. After in vitro fertilization and subsequent culture for 7 days, one blastocyst was obtained from each of the eCG-3, FSH-7 and, FSH-14EA groups, whereas no blastocysts appeared in the other groups. Exogenous gonadotrophins not mouse FSH-stimulated the growing follicles that had developed from the primordial follicles in the xenografts: the effects were incomplete but improved to some extent the meiotic and developmental abilities of the oocytes.

Answer 13:

Bibliographic Information

Estradiol and nicotine exposure enhances A549 bronchioloalveolar carcinoma xenograft growth in mice through the stimulation of angiogenesis. Jarzynka, Michael J.; Guo, Ping; Bar-Joseph, Ifat; Hu, Bo; Cheng, Shi-Yuan. Cancer Institute, Departments of Medicine or Pathology, Research Pavilion at the Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA. International Journal of Oncology (2006), 28(2), 337-344. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 145:60366 AN 2006:150371 CAPLUS

Abstract

Angiogenesis is required for lung cancer growth, which is mediated by various growth factors such as vascular endothelial growth factor (VEGF). Increases in VEGF and angiogenesis have been correlated with poor prognosis and survival in patients with lung cancer. In addn., recent reports show that estradiol and nicotine play important roles in lung tumor initiation and progression. In this report, we demonstrate that estradiol and nicotine exposure enhances the growth of A549 bronchioloalveolar carcinoma xenografts in mice through the stimulation of cell proliferation, VEGF secretion and angiogenesis. We detect a four-fold increase in microvascular d. in tumors from mice exposed to estradiol and nicotine compared to control tumors resulting in an increase in tumor growth. Intriguingly, the effects on angiogenesis and tumor growth by the combination of agents were additive when compared to either agent alone. Furthermore, estradiol promotes VEGF secretion from various non-small cell lung carcinoma (NSCLC) cells and this effect is augmented by nicotine in a tumor xenograft model. These results indicate that aside from their roles in promoting cell proliferation, estradiol and nicotine appear to have additive effects on the induction of angiogenesis through the stimulation of VEGF secretion during NSCLC progression.

Answer 14:

Bibliographic Information

Estradiol regulates different genes in human breast tumor xenografts compared with the identical cells in culture. Harvell, Djuana M. E.; Richer, Jennifer K.; Allred, D. Craig; Sartorius, Carol A.; Horwitz, Kathryn B. Department of Medicine, University of Colorado Health Sciences Center at Fitzsimonas, Aurora, CO, USA. Endocrinology (2006), 147(2), 700-713. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 144:251644 AN 2006:98279 CAPLUS

Abstract

In breast cancers, estrogen receptor (ER) levels are highly correlated with response to endocrine therapies. The authors sought to define mechanisms of estrogen (E) signaling in a solid breast tumor model using gene expression profiling. ER+ T47D-Y human breast cancer cells were grown as xenografts in ovariectomized nude mice under four conditions: 17β-estradiol for 8 wk (E); without E for 8 wk (control); E for 7 wk followed by 1 wk of E withdrawal (Ewd); or E for 8 wk plus tamoxifen for the last week. E-regulated genes were defined as those that differed significantly between control and E and/or between E and Ewd or control and Ewd. These protocols generated 188 in vivo E-regulated genes that showed two major patterns of regulation. Approx. 46% returned to basal states after Ewd (class I genes); 53% did not (class II genes). In addn., more than 70% of class II-regulated genes also failed to reverse in response to tamoxifen. These genes may be interesting for the study of hormone-resistance issues. A subset of in vivo E-regulated genes appears on lists of clin. ER discriminator genes. These may be useful therapeutic targets or markers of E activity. Comparison of in vivo E-regulated genes with those regulated in identical cells in vitro after 6 and 24 h of E treatment demonstrate only 11% overlap. This indicates the extent to which gene expression profiles are uniquely dependent on hormone-treatment times and the cellular microenvironment.

Answer 15:

Bibliographic Information

Anti-angiogenic therapy and chemotherapy affect 99mTc sestamibi and 99mTc-HL91 accumulation differently in tumour xenografts. Kinuya, Seigo; Yokoyama, Kunihiko; Fukuoka, Makoto; Mori, Hirofumi; Shiba, Kazuhiro; Watanabe, Naoto; Shuke, Noriyuki; Michigishi, Takatoshi; Tonami, Norihisa. Department of Biotracer Medicine, Kanazawa University Graduate School of Medical Sciences, Japan. Nuclear Medicine Communications (2005), 26(12), 1067-1073. Publisher: Lippincott Williams & Wilkins, CODEN: NMCODC ISSN: 0143-3636. Journal written in English. CAN 144:225726 AN 2005:1169448 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Favorable effects of cytotoxic chemotherapy for tumors are characterized by the reduced accumulation of radiotracers such as 99mTc sestamibi (MIBI). Anti-angiogenic therapy is primarily cytostatic; consequently, its influence on tracer accumulation may differ from that of cytotoxic treatments. Methods: Anti-angiogenic therapy employing 2-methoxyestradiol was administered in mice bearing s.c. xenografts of LS180 colon cancer cells. The effects of chemotherapy with 5-fluorouracil were examd. as a cytotoxic counterpart. Treatments were conducted for 4 days from day 8. Distribution of 99mTc-MIBI and 99mTc-HL91, a hypoxic marker, was obsd. on days 8 and 12. Oxygen tension (PO2) in tumors was measured by a microelectrode. Cellular uptake of tracers was examd. in vitro in normoxic and hypoxic conditions. Results: 99mTc-MIBI accumulation decreased with increasing tumor wt. when no treatment was conducted. Tumor growth was suppressed by anti-angiogenic therapy and chemotherapy. 99mTc-MIBI accumulation in tumors decreased after chemotherapy as compared to pre-therapeutic values, whereas accumulation of 99mTc-HL91 increased. In contrast, accumulation of tracers did not significantly change after anti-angiogenic therapy as compared to that obsd. pre-therapeutically. Tumor PO2 decreased with increasing tumor vol. when no treatment was conducted. Chemotherapy reduced PO2 in tumors. PO2 in tumors treated with anti-angiogenic therapy was as high as that obsd. before treatment. 2-Methoxyestradiol or 5-fluorouracil did not significantly affect tracer accumulation in cells under both normoxic and hypoxic conditions in vitro. Conclusion: These findings indicate that scintigraphic assessment of therapeutic efficacy of anti-angiogenic therapy should be performed from a perspective distinct from that of cytotoxic treatment.

Answer 16:

Bibliographic Information

In vitro and in vivo antitumorigenic activity of a mixture of lysine, proline, ascorbic acid, and green tea extract on human breast cancer lines MDA-MB-231 and MCF-7. Roomi, M. Waheed; Ivanov, Vadim; Kalinovsky, Tatiana; Niedzwiecki, Aleksandra; Rath, Matthias. Cancer Research Division, Matthias Rath Research, Santa Clara, CA, USA. Medical Oncology (Totowa, NJ, United States) (2005), 22(2), 129-138. Publisher: Humana Press Inc., CODEN: MONCEZ ISSN: 1357-0560. Journal written in English. CAN 143:415700 AN 2005:862477 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Current treatments are generally ineffective once breast cancer has metastasized; median survival is reduced to 2-3 yr. Previous research studies demonstrating potent synergistic antitumor activity of lysine, proline, ascorbic acid, and epigallocatechin gallate prompted us to investigate the in vivo inhibitory effect of a nutrient mixt. contg. lysine, proline, arginine, ascorbic acid, and epigallocatechin gallate (NM) on the growth of human cancer xenografts in female athymic nude mice. Five to six week old female mice were inoculated with 3×106 breast cancer cells MDA-MB-231. After injection, the mice were randomly divided into two groups A and B; group A was fed a regular diet and group B with the regular diet supplemented with 0.5% of the nutrient mixt. (NM). Four weeks later, the mice were sacrificed, and their tumors were excised, weighed, and processed for histol. We also tested the effect of NM in vitro on estrogen-receptor pos. (ER+) MCF-7 and estrogen-receptor neg. (ER-) MDA-MB-231 breast cancer cell lines by measuring: cell proliferation by MTT assay, expression of MMPs by gelatinase zymog., invasion through Matrigel, and VEGF by ELISA. MCF-7 cells were also treated with estradiol to study enhanced invasion and expression of MMPs and VEGF. Results showed that NM inhibited the growth and reduced the size of tumors in female nude mice by 27%. Furthermore, histol. evaluation revealed increased mitotic index, MMP-9 and VEGF secretion, and PAS material (mucin) in the control group tissues. In vitro studies showed NM inhibited MDA-MB-231 cell growth by 34% at 500 μg/mL and MCF-7 cell growth by 18% at 1000 μg/mL. Invasion of MDA-MB-231 through Matrigel was inhibited by 50%, 60%, and 95% by 10, 50, and 100 μg/mL of NM, resp. The results of this study demonstrated that the nutrient mixt. tested significantly suppressed tumor growth of breast cancer cells in female athymic nude mice and significantly inhibited MMP expression, angiogenesis, and invasion in breast cancer cells, in vitro, offering promise for therapeutic use in the treatment of breast cancer.

Answer 17:

Bibliographic Information

Stimulation of MCF-7 tumor progression in athymic nude mice by 17β-estradiol induces WISP-2/CCN5 expression in xenografts: A novel signaling molecule in hormonal carcinogenesis. Ray, Gibanananda; Banerjee, Snigdha; Saxena, Neela K.; Campbell, Donald R.; Van Veldhuizen, Peter; Banerjee, Sushanta K. Cancer Research Unit, V.A. Medical Center, University of Missouri, Kansas City, MO, USA. Oncology Reports (2005), 13(3), 445-448. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 143:75716 AN 2005:240503 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

There was 100% solid tumor formation following inoculation of MCF-7 cells. However, MCF-7 tumor progression was significantly greater in the mice exposed to 17β-estradiol (17β-E2) compared to unexposed mice. WISP-2/CCN5 mRNA expression was correspondingly increased in 17β-E2 exposed MCF-7 tumors compared to unexposed xenografts. Moreover, estrogen exposure followed by anti-estrogen tamoxifen treatment drastically inhibited the tumor growth and WISP-2 expression in nude mice. Therefore, the study suggests that higher WISP-2/CCN5 expression by estrogen may be assocd. with the estrogen-induced growth of MCF-7 tumors in vivo. Finally, overexpression of WISP-2/CCN5 may be considered as a prognostic marker of estrogen-sensitive tumor growth.

Answer 18:

Bibliographic Information

Nude Mice as a Model for Gonadotropin-Induced Adrenocortical Neoplasia. Bielinska, M.; Genova, E.; Boime, I.; Parviainen, H.; Kiiveri, S.; Rahman, N.; Leppaeluoto, J.; Heikinheimo, M.; Wilson, D. B. Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA. Endocrine Research (2004), 30(4), 913-917. Publisher: Taylor & Francis, Inc., CODEN: ENRSE8 ISSN: 0743-5800. Journal written in English. CAN 143:75614 AN 2005:18606 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Certain inbred mice (e.g., DBA/2J, CE) develop sex steroid producing adrenocortical tumors following gonadectomy. This adrenal

response is thought to result from an unopposed increase in circulating gonadotropins and/or a decrease in factor(s) of gonadal origin. To differentiate between these two possibilities, we utilized the NU/J strain of nude mice, which are immunol. compromised and therefore permissive to xenografts. One group of female nude mice was gonadectomized, while another group of females received xenografts of CHO cells stably transfected with human chorionic gonadotropin (hCG). After 1-2 mo, subcapsular adrenocortical neoplasms contg. sex steroid-producing cells were obsd. in both groups. We conclude that high levels of circulating gonadotropins are sufficient to induce adrenocortical tumorigenesis, even in the presence of intact gonads.

Answer 19:

Bibliographic Information

Human endometriotic xenografts in immunodeficient RAG-2/γ(c)KO mice. Greenberg, Laura H.; Slayden, Ov D. Department of Obstetrics and Gynecology, Providence St. Vincent Hospital, Portland, OR, USA. American Journal of Obstetrics and Gynecology (2004), 190(6), 1788-1796. Publisher: Elsevier Inc., CODEN: AJOGAH ISSN: 0002-9378. Journal written in English. CAN 141:258711 AN 2004:630435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective: The purpose of this study was to create a novel animal model for studies of endometriosis. Study design: To facilitate the study of the transplantation of endometriosis into immunodeficient RAG-2/γ(c)KO mice, endometriosis biopsy specimens were collected from 19 women by laparoscopic surgery and grafted s.c. into the mice, which were treated subsequently with estradiol and progesterone to create 28-day artificial cycles. The grafts were collected during the first, second, and fourth cycles and were evaluated histol. for evidence of bleeding and immunocytochem. for estrogen receptor and progesterone receptor. Results: Biopsy specimens that contained endometrium-like glands were well accepted (> 90% success). These grafts maintained glandular morphol. condition, estrogen receptor, and progesterone receptor; bled after progesterone withdrawal; and formed chocolate cysts. However, biopsy specimens that lacked glands or that consisted of peritoneal adhesions and stroma were accepted poorly (< 5% success) and failed to show evidence of estrogen receptor, progesterone receptor, or cyclic bleeding. Conclusion: Human endometriosis transplanted into RAG-2/γ(c)KO mice can provide a model for endometriotic bleeding.

Answer 20:

Bibliographic Information

Estrogen Receptor β Inhibits Human Breast Cancer Cell Proliferation and Tumor Formation by Causing a G2 Cell Cycle Arrest. Paruthiyil, Sreenivasan; Parmar, Hema; Kerekatte, Vaishali; Cunha, Gerald R.; Firestone, Gary L.; Leitman, Dale C. Departments of Obstetrics, Gynecology, and Repoductive Sciences, Cellular and Molecular Pharmacology, Center for Reproductive Sciences, University of California, San Francisco, San Francisco, CA, USA. Cancer Research (2004), 64(1), 423-428. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 140:143695 AN 2004:47895 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Studies indicate that estrogen receptor (ER) α mediates breast cancer-promoting effects of estrogens. The role of ERβ in breast cancer is unknown. Elucidating the role of ERβ in the pathogenesis of breast cancer is important because many human breast tumors express both ERα and ERβ. We show that adenovirus-mediated expression of ERβ changes the phenotype of ERα-pos. MCF-7 cells. Estradiol increases cell proliferation and causes tumor formation of MCF-7 cells expressing only ERα. In contrast, introducing ERβ into MCF-7 cells causes an inhibition of proliferation in vitro and prevents tumor formation in a mouse xenograft model in response to estradiol. ERβ inhibits proliferation by repressing c-myc, cyclin D1, and cyclin A gene transcription, and increasing the expression of p21Cip1 and p27Kip1, which leads to a G2 cell cycle arrest. These results demonstrate that ERα and ERβ produce opposite effects in MCF-7 cells on cell proliferation and tumor formation. Natural or synthetic ERβ-selective estrogens may lack breast cancer promoting properties exhibited by estrogens in hormone replacement regimens and may be useful for chemoprevention of breast cancer.

Answer 21:

Bibliographic Information

Paradoxical Action of Fulvestrant in Estradiol-Induced Regression of Tamoxifen-Stimulated Breast Cancer. Osipo, Clodia; Gajdos, Csaba; Liu, Hong; Chen, Bin; Jordan, V. Craig. Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA. Journal of the National Cancer Institute (2003), 95(21), 1597-1608. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 140:280903 AN 2003:903987 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Long-term tamoxifen treatment of breast cancer can result in tamoxifen-stimulated breast cancer, in which estrogen inhibits tumor growth after tamoxifen withdrawal. The authors investigated the mol. mechanism(s) of estradiol-induced tumor regression by using an in vivo model of tamoxifen-stimulated human breast cancer. Methods: Growth of parental estradiol-stimulated MCF-7E2 and long-term tamoxifen-stimulated MCF-7TAMLT xenografts in athymic mice was measured during treatment with vehicle, estradiol, estradiol plus tamoxifen, tamoxifen alone, estradiol plus fulvestrant, or fulvestrant alone. Apoptosis was detected by the terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay. Protein expression was assessed by western blot anal. mRNA expression was assessed by real-time reverse transcription-polymerase chain reaction. All statistical tests were two-sided. Results: MCF-7E2 tumor growth was stimulated by estradiol (cross-sectional area at week 13=1.06 Cm2, 95% confidence interval [CI] = 0.82 to 1.30 Cm2; P<.001) compared with control (0.06 Cm2, 95%CI = -0.02 to 0.14 Cm2), but tumor growth was inhibited by tamoxifen or fulvestrant. MCF-7TAMLT tumor growth was stimulated by tamoxifen (cross-sectional area at week 10=0.60 Cm2, 95% CI = 0.50 to 0.70 Cm2; P<.001) compared with control (0.02 Cm2, 95% CI = 0.00 to 0.04 Cm2). For MCF-7TAMLT tumors that were initially 0.35 Cm2, estradiol-induced regression to 0.18 Cm2 (95% CI = 0.15 to 0.21 Cm2; P<.001), and tamoxifen or estradiol plus fulvestrant enhanced tumor growth to 1.00 Cm2 (95% CI = 0.88 to 1.22 Cm2). Estradiol increased the no. of apoptotic cells in tumors by 23% (95% CI = 20% to 26%; P<.001) compared with all other treatments, decreased estrogen receptor α (ERα) protein expression, increased the expression of Fas mRNA and protein, decreased the expression of HER2/neu mRNA and protein and nuclear factor κB (NF-κB) protein but did not affect Fas ligand protein expression compared with control.

Paradoxically, fulvestrant reversed this effect and stimulated MCF-7TAMLT tumor growth apparently through ERα-mediated regulation of Fas, HER2/neu, and NF-κB. Conclusion: Physiol. levels of estradiol induced regression of tamoxifen-stimulated breast cancer tumors, apparently by inducing the death receptor Fas and suppressing the antiapoptotic/prosurvival factors NF-κB and HER2/neu.

Answer 22:

Bibliographic Information

Inhibition of androgen-independent growth of prostate cancer xenografts by 17β-estradiol. Corey, Eva; Quinn, Janna E.; Emond, Mary J.; Buhler, Kent R.; Brown, Lisha G.; Vessella, Robert L. Departments of Urology, University of Washington, Seattle, WA, USA. Clinical Cancer Research (2002), 8(4), 1003-1007. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 137:73517 AN 2002:359635 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Estrogen treatment has long been known to be of benefit in prostate cancer (CaP), but its mechanism was thought to involve merely a redn. in androgen levels. However, new evidence indicates that estrogen may exert effects on CaP cells in the absence of androgens. Implantation of CaP xenografts (LuCaP 35, LuCaP 49, LuCaP 58, LuCaP 73, PC-3, and LNCaP) into intact and ovariectomized female mice was done to characterize growth and take rates in the absence of androgens. Ovariectomized female mice were supplemented with 17β-estradiol, and LuCaP 35 CaP xenograft take and growth rates were detd. Reverse transcription-PCR was used to evaluate the presence of the estrogen receptor messages in CaP xenografts. The authors have obsd. significant inhibition of CaP growth in intact vs. ovariectomized female animals in five of six CaP xenograft lines. 17β-Estradiol supplements given to ovariectomized female mice led to inhibition of tumor establishment and diminished growth of LuCaP 35 similar to that obsd. in

intact female mice. Using reverse transcription-PCR, the authors have shown that these xenografts express the estrogen receptor β message. The authors have detd. that 17β-estradiol supplementation causes inhibition of CaP growth in an animal model by mechanisms that are independent of androgen action. This gives rise to the possibility that estrogen therapy may be of potential use with hormone-refractory cancers. The xenograft models the authors describe herein may be useful as well in elucidating the pathways mediating the androgen-independent effects of estrogen on CaP.

Answer 23:

Bibliographic Information

Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor α and β and show biological responses to estrogen. Stabile, Laura P.; Davis, Autumn L. Gaither; Gubish, Christopher T.; Hopkins, Toni M.; Luketich, James D.; Christie, Neil; Finkelstein, Sydney; Siegfried, Jill M. Department of Pharmacology, Lung Cancer Program, University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA, USA. Cancer Research (2002), 62(7), 2141-2150. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 137:15937 AN 2002:288697 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Lung cancer is becoming increasingly common in women and in the United States accounts for more female cancer deaths annually than breast cancer. Many epidemiol. studies have provided evidence that women are more susceptible than men to the adverse effects of tobacco smoke. These observations suggest the possible role of estrogens in lung carcinogenesis. The authors report the expression of mRNA for estrogen receptor α (ERα) and β (ERβ) in cultured human non-small cell lung cancer cells, cultured lung fibroblasts, and primary cultures of normal bronchial epithelium. Western anal. of ERα suggested that the main protein expressed in lung tumor cells is a variant, probably attributable to alternative splicing. Protein for ERβ was found to be a mixt. of full-length as well as alternatively spliced variants. β-Estradiol produced a proliferative response in vitro in both normal lung fibroblasts and cultured non-small cell lung tumor cells. This effect was also obsd. in vivo. In this regard, β-estradiol stimulated growth of the non-small cell lung tumor line, H23, grown as tumor xenografts in SCID mice. This effect was blocked by fluvestrant (ICI 182,780). In paraffin sections of non-small cell lung tumors, ERβ immunoreactivity was localized to the nucleus, whereas ERα immunoreactivity was mainly localized to the cytoplasm, suggesting that both nuclear and cytoplasmic signaling may be involved in estrogenic responses in the lung. To show that the ERs found in the lung are functional, the authors demonstrated that β-estradiol stimulated transcription of an estrogen response element-luciferase construct transfected in non-small cell lung tumor cell lines. Antiestrogens blocked this effect. Treatment of lung fibroblasts with β-estradiol also increased secretion of hepatocyte growth factor by 2-fold. These results suggest that estrogen signaling plays a biol.

role in both the epithelium and the mesenchyme in the lung and that estrogens could potentially promote lung cancer, either through direct actions on preneoplastic or neoplastic cells or through indirect actions on lung fibroblasts. Addnl., it is possible that antiestrogens may have therapeutic value to treat or prevent lung cancer.

Answer 24:

Bibliographic Information

Effects of a pure antiestrogen on apoptosis and proliferation within human breast ductal carcinoma in situ. Gandhi, Ashu; Holland, Philip A.; Knox, W. Fiona; Potten, Christopher S.; Bundred, Nigel J. University Department of Surgery, University Hospital of South Manchester, Manchester, UK. Cancer Research (2000), 60(15), 4284-4288. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 133:217912 AN 2000:597775 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adjuvant antiestrogen (AE) therapy has been proposed for all women with ductal carcinoma in situ (DCIS). However, many cases of DCIS are of the high-grade, estrogen receptor (ER)-neg. subtype that are unlikely to respond to AE treatment. Hormonal agents work

by increasing apoptosis and/or decreasing cell proliferation; therefore, the authors studied the effect of a pure AE on levels of apoptosis and proliferation in human DCIS xenografts using an in vivo model. Women (n = 23) with mammog. microcalcification suggestive of DCIS were identified at the time of surgery (day 0), a sample of representative tissue was obtained, divided into multiple 2 × 2 × 1-mm xenografts, and implanted s.c. into female BALB/c nu/nu mice (eight xenografts/mouse). Day 0 grafts underwent immunohistochem. assessment of ER status. Fourteen days after implantation, four xenografts were retrieved and mice were randomly divided into one of three treatment groups: (a) insertion of a slow release 2-mg 17β-estradiol pellet; (b) weekly 5-mg injections of the pure AE Faslodex (Zeneca Pharmaceuticals); and (c) injections of a control vehicle oil alone. After 2 wk of treatment, the remaining four xenografts were retrieved from each mouse. Retrieved xenografts contg. DCIS were assessed for morphol. evidence of apoptotic cell death [apoptotic index (AI)] and cell proliferation (by immunohistochem. detection of the Ki67 proliferation antigen LI). Both AI and LI were higher in the day 0 specimens of 16 ER - DCIS lesions compared with 7 ER+ DCIS lesions (mean values, 1.47% vs. 0.32% and 20.6% vs. 3.1%; both P < 0.0001). AI and LI values within ER- DCIS did not differ between xenografts exposed to 17β-estradiol or AE treatment compared with the controls or pretreatment values (mean AI and LI in estradiol-treated, antiestrogen-treated, and control groups 1.04% vs. 0.98% vs. 1.29% and 17.2% vs. 20.5% vs. 17.7% resp.). In contrast, treatment of mice bearing ER+ DCIS xenografts with 17β-estradiol raised both the AI (1.03% vs.
0.40%, P = 0.03) and LI (11.0% vs. 5.1%, P = 0.007) compared with controls. AE therapy of ER+ DCIS xenografts did not affect proliferation but resulted in higher apoptosis than in controls (0.9% vs. 0.4% resp., P = 0.04). AE therapy should be reserved for patients with estrogen receptor-pos. DCIS.

Answer 25:

Bibliographic Information

Estradiol hypersensitivity and mitogen-activated protein kinase expression in long-term estrogen deprived human breast cancer cells in vivo. Shim, Woo-Shin; Conaway, Mark; Masamura, Shigeru; Yue, Wei; Wang, Ji-Ping; Kumar, Rakesh; Santen, Richard J. Department of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, VA, USA. Endocrinology (2000), 141(1), 396-405. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 132:117760 AN 2000:4779 CAPLUS

Abstract

Women with breast cancer who have responded to initial hormonal therapy frequently experience addnl. remissions upon further endocrine manipulation. The authors postulate that hypersensitivity to estradiol (E2) may serve as a mechanistic explanation for these secondary responses. The authors previously provided evidence of hypersensitivity using an in vitro breast cancer model system and demonstrated the role of mitogen-activated protein kinase (MAP kinase) in the process of adaptation to long-term estradiol deprivation. In the present study, the authors wished to demonstrate that hypersensitivity to E2 could occur under more complex in vivo conditions and that MAP kinase activation is enhanced under these circumstances. The authors used an MCF-7 breast cancer model system involving long-term estradiol deprived (LTED) cells to produce xenografts in nude mice and an E2 clamp method to precisely control sex steroid levels. The E2 clamp was designed to maintain plasma E2 at a series of doubling doses from 1.25 pg/mL to 20.0 pg/mL in oophorectomized nude mice. As evidence of the validity of the clamp method, a uterine wt. bioassay revealed an excellent, linear dose-response relationship between the predicted level of plasma E2 and stimulation of uterine wt. As evidence of hypersensitivity, we found that LTED xenograft tumors grew to a greater extent than wild-type in response to E2 concns. of 1.25pg/mL (P = 0.003) and 2.5 pg/mL (P = 0.0002). At the 10.0 and 20.0 pg/mL plasma concns., the LTED tumors were stimulated to a lesser extent than the wild-type. This pattern of increased growth at lower concns. and reduced growth vs. the wild-type at higher concns. mimics closely the pattern seen for LTED cells in vitro. All LTED cell tumors exhibited enhanced activation of MAP kinase ranging from 18 to 25%, and E2 did not increase this further. In contrast, E2 caused a linear increase in the percentage of activated MAP kinase pos.

cells (P < 0.0001) in wild-type tumors from basal levels of 2.66% to maximal levels of 6.40%. These observations suggest a dynamic interplay whereby activation of MAP kinase renders cells more sensitive to the proliferative effects of E2. The precise mechanisms for this interplay are unknown but, when further understood, could potentially provide insight into approaches to prevent the evolution of tumors to a hormone insensitive state.

Answer 26:

Bibliographic Information

Expression of CD44 isoforms in human breast carcinoma xenografts is not influenced by the treatment of mice with cytostatics or (anti-)hormones. Dehmel, A.; Becker, M.; Lemm, M.; Fichtner, I. Max-Delbruck-Center of Molecular Medicine, Berlin, Germany. Anticancer Research (1999), 19(3A), 1977-1987. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 132:120767 AN 1999:654678 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

CD44 std. (s) and variant (v) isoforms have been discussed to be implicated in progression and metastasis of different malignomas. For breast carcinomas, the results of different studies are contradictory. These apparent discrepancies suggest that CD44 isoforms are not available on the tumor cell surface, but could be regulated by different endogenous and exogenous factors. Here we report the regulation of CD44 isoforms in xenografted breast cancer cell lines by cytostatics, hormones and antihormones. The human breast cancer models MDA-MB 435, MCF-7, NCI/ADR, 4296, 4151 and 4134 were transplanted into the mammary fat pad of nude mice. When tumors reached a palpable size, animals were treated with farmorubicin, cyclophosphamide, estradiol, tamoxifen or progesterone, resp. At different times after treatment, serum and tumors were taken. The expression of CD44 and its isoforms was detd. by immunohistochem. and RT-PCR, serum levels were measured by human specific ELISA kits. Serum levels of CD44s and v6 varied among the tumors. For 3/6 tumors we found differences between control groups and treated animals. Immunohistochem. results remained unchanged: each tumor showed a specific pattern of CD44 expression, but this pattern did not change when the animals received cytostatics, hormones or antihormones. The same held true for RT-PCR-results. Also, the time of tumor collection had no influence on CD44 expression. Therefore, it can be concluded, that in the xenografted breast cancer cell lines a regulation of CD44 isoforms by farmorubicin, cyclophosphamide, estradiol, progesterone or tamoxifen could not be found, while serum levels were influenced in some cases probably due to tumor cell kill and shedding of surface proteins into blood stream.

Answer 27:

Bibliographic Information

Effect of TCDD on the transient suppression of estrogen-dependent MCF-7 human breast tumor growth in vivo. Gierthy, John F.; Bennett, James A.; Spink, Barbara C.; Spink, David C.; Arcaro, Kathleen F.; Vakharia, Dilip D. Wadsworth Center, New York State Department Health, Albany, NY, USA. Organohalogen Compounds (1998), 37(Toxicology, Endocrine Disruption, Metabolism and Kinetics), 257-260. Publisher: ECO-INFORMA Press, CODEN: ORCOEP ISSN: 1026-4892. Journal written in English. CAN 130:34347 AN 1998:804316 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The mechanistic basis of a transient suppression of 17β-estradiol (E2)-dependent breast tumor xenograft growth in mice was investigated. The transient suppression was induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Pretreatment with TCDD (5 μg/kg body wt.) for 2 wk prior to tumor implantation and E2 supplementation eradicated the TCDD suppressive effects of E2 stimulated tumor growth. Mice were exposed to TCDD without E2 supplementation applying both the 2-wk pre-implant exposure followed by 3-wk post-implant exposure as well as the 3-wk post-implant exposure. No increase in tumor growth compared to the usual E2-dependent growth and transient TCDD-suppressed tumor growth was shown. Tumors from mice treated with TCDD for 3 wk and exhibiting TCDD resistant, E2-dependent growth were transplanted into naive mice followed by the usual E2 supplementation and TCDD treatment. Tumor again demonstrated E2 growth dependency as well as the 2-wk transient TCDD suppression of growth obsd. in the original implantation expts. The results showed a TCDD-mediated change in the mouse host rather than in the tumor.

Answer 28:

Bibliographic Information

Melatonin does not inhibit estradiol-stimulated proliferation in MCF-7 and BG-1 cells. Baldwin, William S.; Travlos, Gregory

S.; Risinger, John I.; Barrett, J. Carl. Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, USA. Carcinogenesis (1998), 19(11), 1895-1900. Publisher: Oxford University Press, CODEN: CRNGDP ISSN: 0143-3334. Journal written in English. CAN 130:105546 AN 1998:784483 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Melatonin, an indolic pineal hormone, is produced primarily at night in mammals and is important in controlling biol. rhythms. Previous research suggested that melatonin can attenuate proliferation in the estrogen-responsive MCF-7 breast cancer cell line. We tested whether these anti-proliferative effects may have physiol. consequences upon two estrogen-responsive cell lines, MCF-7 (a breast cancer cell line) and BG-1 (an ovarian adenocarcinoma cell line). Melatonin (10-9-10-5 M) attenuated proliferation of MCF-7 and BG-1 cells by >20% in the absence of estrogen. However, 17β-estradiol exposure negated the ability of melatonin to inhibit proliferation. To substantiate this finding, cells were estrogen starved followed by multiple treatments with estradiol and melatonin. Melatonin did not inhibit estradiol-stimulated proliferation under this protocol. Estradiol increased MCF-7 and BG-1 cell cycle transition from G1 to S phase, however, melatonin did not inhibit this transition nor did it down-regulate estradiol-induced pS2 mRNA levels measured by northern blotting, further indicating that melatonin was unable to attenuate estradiol-induced proliferation and gene expression. We also examd. the effects of melatonin on estradiol-induced proliferation in MCF-7 cell xenografts in athymic nude mice. Melatonin at a dose 28 times greater than 17β-estradiol did not inhibit estradiol-induced proliferation in vivo. Furthermore, pinealectomy did not increase proliferation. Therefore, we conclude that melatonin does not directly inhibit estradiol-induced proliferation.

Answer 29:

Bibliographic Information

α-Fetoprotein derived from a human hepatoma prevents growth of estrogen-dependent human breast cancer xenografts. Bennett, James A.; Zhu, ShuJi; Pagano-Mirarchi, Andrea; Kellom, Theresa A.; Jacobson, Herbert I. Albany Medical College, Albany, NY, USA. Clinical Cancer Research (1998), 4(11), 2877-2884. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 130:162836 AN 1998:767396 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

α-Fetoprotein (AFP) is a transport protein that has growth-regulatory properties in many different tissues. It is known to interfere with responses stimulated by estrogen. The purpose of this study was to det. whether human AFP would inhibit the growth of human breast cancer. AFP was isolated from the culture supernatant of human hepatoma cells (HepG2) grown in serum-free medium and was purified by immunoaffinity chromatog. Human breast cancers were grown as xenografts under the kidney capsule of severe combined immunodeficient mice. The min. ID of AFP against estradiol (E2)-stimulated growth of human MCF-7 breast cancer xenografts was 10 μg/mouse/day, and max. inhibition (no growth) was achieved with 100 μg/mouse/day. Daily treatment was required to sustain inhibition. This 100-μg dose of AFP also inhibited xenograft growth of E2-dependent T47 human breast carcinoma. Estrogen receptor-neg. MDA MB 231 and BT20 human breast carcinoma xenografts were not inhibited by AFP (100 μg/mouse/day). Elevation in serum E2 occurred during AFP treatment. AFP did not compete with agonists for the estrogen receptor. These lab. results are consistent with the findings of a literature search, which consistently showed an assocn. between elevated pregnancy levels of AFP and subsequent reduced risk for breast cancer later in life. We conclude that AFP can inhibit growth of estrogen-dependent breast cancer and warrants further development as an agent for the treatment and perhaps even the prevention of human breast cancer.

Answer 30:

Bibliographic Information

Hormonal regulation of epidermal growth factor receptor content and signaling in bovine mammary tissue. Sheffield, Lewis G. Dairy Science Department, University of Wisconsin, Madison, WI, USA. Endocrinology (1998), 139(11), 4568-4575. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 130:47888 AN 1998:711659

CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Mammary tissue from midpregnant heifers was cultured with epidermal growth factor (EGF) or transforming growth factor α for 1-3 days. After 1 day, 10 nM EGF or transforming growth factor α doubled DNA synthesis, whereas lower concns. (0.1 or 1 nM) increased DNA synthesis 2- to 3-fold after 2-3 days in culture. In other studies, bovine mammary tissue was transplanted to ovariectomized athymic mice and treated for 10 days with saline, estradiol (1 μg/day), progesterone (1 mg/day), or estradiol + progesterone. Subsequent explant culture of the bovine tissue indicated that estradiol + progesterone augmented the ability of EGF to stimulate DNA synthesis. The increased response to EGF was assocd. with increased EGF binding and with increased EGF-induced tyrosine kinase that paralleled the increased EGF binding. In other studies, athymic mice bearing xenografted bovine mammary tissue were primed for 10 days with estradiol and progesterone, followed by 2-day treatment with saline (control), hydrocortisone (200 μg/day), PRL (1 mg/day), or hydrocortisone + PRL. Hydrocortisone and PRL alone decreased, and PRL + hydrocortisone eliminated, EGF-induced DNA synthesis. EGF receptor content was unaffected by hydrocortisone but was reduced by PRL or hydrocortisone + PRL. Furthermore, the ability of EGF to induce tyrosine kinase activity was decreased by PRL and by hydrocortisone + PRL. The decreased kinase activity was greater than the decrease in receptor binding, suggesting a specific modulation of EGF receptor kinase activity in response to lactogenic hormones.

Answer 31:

Bibliographic Information

Apoptotic regression of MCF-7 xenografts in nude mice treated with the vitamin D3 analog, EB1089. Vanweelden, Kathryn; Flanagan, Louise; Binderup, Lise; Tenniswood, Martin; Welsh, Joellen. W. Alton Jones Cell Science Center, Lake Placid, NY, USA. Endocrinology (1998), 139(4), 2102-2110. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 128:304391 AN 1998:206694 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

1,25-Dihydroxyvitamin D3[1,25-(OH)2D3] and its synthetic analog EB1089 induce characteristic morphol. features of apoptosis in MCF-7 cells in vitro that coincide with up-regulation of clusterin and cathepsin B, proteins assocd. with apoptosis in the mammary gland, and with down-regulation of Bcl-2, an antiapoptotic protein. To det. whether vitamin D3 compds. could mediate apoptosis of breast tumors in vivo, the authors treated nude mice carrying established MCF-7 xenografts with the low calcemic vitamin D3 analog EB1089 via daily injection or sustained release pellets for up to 5 wk. The vol. of tumors from mice treated with 45 pmol/day EB1089 was 4-fold lower than that of tumors from vehicle-treated control mice after 5 wk. The reduced growth of tumors from EB1089-treated mice was assocd. with characteristic apoptotic morphol. and a marked redn. in the proportion of epithelial cells to stroma. After 5 wk of treatment with EB1089, MCF-7 tumors exhibited a 6-fold increase in DNA fragmentation (as measured by in situ end labeling) relative to that in control tumors. The enhanced rate of apoptosis in tumors from EB1089-treated mice was coupled to a 2-fold redn. in proliferation (as measured by expression of proliferating cell nuclear antigen) compared with that in tumors from control mice. The antitumor effects of EB1089 were evident at doses that had minimal effects on serum calcium and body wt. EB1089 treatment did not alter the growth of xenografts derived from a vitamin D3-resistant variant of MCF-7 cells (MCF-7D3Res cells), which display resistance to EB1089 in vitro, indicating that resistance to EB1089 is maintained in vivo. Tumors derived from both MCF-7 and MCF-7D3Res cells underwent apoptotic regression upon estradiol withdrawal, indicating comparable estrogen dependence of tumors with differential sensitivity to vitamin D3 compds. These are the first studies to demonstrate apoptotic morphol.

and regression of human breast tumors in response to treatment with a vitamin D3 analog in vivo and support the concept that vitamin D3 compds. can effectively target human breast cancer.

Answer 32:

Bibliographic Information

Estradiol induces DNA fragmentation in a human endometrial adenocarcinoma with estradiol-inhibited growth phenotype.

Karlsson, Lena; Leser, Gunilla; Ryd, Walter; Horvath, Gyorgy. Research Laboratory, Department of Oncology, Sahlgrenska University Hospital, Goeteborg, Swed. Anticancer Research (1997), 17(5A), 3259-3263. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 128:123893 AN 1998:49676 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A moderately differentiated human endometrial adenocarcinoma heterotransplanted into nude mice was investigated for morphol. and mol. changes in the tumors after treating the animals with estradiol. The tumor growth was previously characterized as estradiol-independent but responsive (inhibited) without any changes in cell proliferation. In response to hormonal treatment rather the cell loss factor increased. In this expt. tumors influenced by estradiol were investigated at different time-points after treatment by an in situ labeling technique to detect cells undergoing DNA fragmentation as a sign of apoptosis. Expression of the apoptosis related protein bcl-2 was evaluated by Western blotting. Tumors from animals treated with estradiol showed an increase in tumor vol. doubling time from 5.4 days to 16 days compared to control tumors. Histol., tumors influenced by estradiol were better differentiated than control tumors and showed a significant increase in cells staining pos. with the in situ apoptosis detection technique. A parallel time dependent decreased expression of bcl-2 protein was obsd. These results confirm our previous findings where estradiol influenced the cell loss factor without changes in the growth fraction, indicating increased apoptotic activity in response to hormonal treatment.

Answer 33:

Bibliographic Information

Estrogen sensitivity of normal human breast tissue in vivo and implanted into athymic nude mice: analysis of the relationship between estrogen-induced proliferation and progesterone receptor expression. Clarke, Robert B.; Howell, Anthony; Anderson, Elizabeth. Clinical Research Department, Christie Hospital NHS Trust, Manchester, UK. Breast Cancer Research and Treatment (1997), 45(2), 121-133. Publisher: Kluwer, CODEN: BCTRD6 ISSN: 0167-6806. Journal written in English. CAN 127:341996 AN 1997:698379 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

High serum concns. of estradiol (E2) equiv. to those obsd. in the luteal phase of the menstrual cycle stimulate both epithelial cell proliferation and progesterone receptor (PgR) expression in normal human breast tissue xenografted into athymic nude mice. The authors report the results of further investigations designed to det. whether the induction of PgR expression and proliferation require different E2 concns. and whether proliferating cells expressed the PgR. In untreated normal breast xenografts, the PgR was virtually undetectable and proliferation was at basal levels. Progesterone (Pg) treatment alone had no effect compared to no treatment. Treatment with E2 at follicular phase serum concns. maximally increased PgR expression but was without effect on proliferation. However, treatment with E2 at luteal phase serum concns., alone or in combination with Pg, significantly increased both the PgR content and the proliferation of the breast epithelium. These exptl. derived data reflected the observations made on normal breast tissue at surgical biopsy where PgR content was similar in both halves of the menstrual cycle, whereas proliferation was significantly higher in the luteal phase. Finally, using double labeling techniques, it was demonstrated that proliferating epithelial cells rarely expressed PgR in normal breast tissue obtained at surgical biopsy. These results suggest that the threshold of E2 required to induce PgR expression in normal human breast epithelial cells is lower than that required to induce proliferation and that the majority of proliferating breast cells do not express the PgR.

Answer 34:

Bibliographic Information

Type I insulin-like growth factor receptor gene expression in normal human breast tissue treated with estrogen and progesterone. Clarke, R. B.; Howell, A.; Anderson, E. Clinical Research Department, Manchester, UK. British Journal of Cancer (1997), 75(2), 251-257. Publisher: Churchill Livingstone, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 126:152968 AN 1997:115721 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The epithelial proliferation of normal human breast tissue xenografts implanted into athymic nude mice is significantly increased from basal levels by estradiol (E2), but not progesterone (Pg) treatment at serum concns. similar to those obsd. in the luteal phase of the human menstrual cycle. Type I IGF receptor (IGFR-I) mRNA and protein have been shown to be up-regulated by E2 in MCF-7 breast cancer cells in vitro in which IGF-I and E2 act synergistically to stimulate proliferation. We have investigated the expression of the IGFR-I mRNA in normal human breast xenografts treated with or without E2 or Pg alone and in combination. Northern anal. of 20 μg of RNA extd. from the breast xenograft samples showed no hybridization with 32P-labeled IGFR-I probe, although an 11-kb species of IGFR-I mRNA could be seen when 20 μg of RNA extd. from either MCF-7 breast cancer cells or human breast carcinomas was examd. in this way. To analyze the expression of IGFR-I mRNA in breast xenografts, a quant. reverse transcription - polymerase chain reaction (RT-PCR) was employed in which RNA loading, reverse transcription and PCR efficiencies were internally controlled. The data indicate that the IGFR-I mRNA is up-regulated by two to threefold compared with untreated levels by 7 and 14 days E2 treatment. In contrast, 7 or 14 days Pg treatment down-regulates the receptor mRNA to approx. half that of untreated levels, whereas combination E2 and Pg treatment a twofold increase in IGFR-I mRNA levels compared with untreated tissue. The results are consistent with the suggestion that E2 may act to stimulate proliferation indirectly via a paracrine mechanism involving IGFs in normal as well as malignant human breast epithelial cells.

Answer 35:

Bibliographic Information

Estradiol influences p53 expression in a human endometrial adenocarcinoma heterotransplanted into nude mice. Horvath, Gyoergy; Leser, Gunilla; Delle, Ulla. Division Gynaecological Oncology, Sahlgrenska University Hospital, Goeteborg, Swed. In Vivo (1996), 10(1), 29-32. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 125:54998 AN 1996:373745 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The influence of different estradiol concns. on the expression of the p53 suppressor gene and on cell kinetics was examd. by semiquant. anal. of protein and bromodeoxyuridine labeling in a human endometrial adenocarcinoma grown in nude mice. We found that increasing the circulating estradiol increases, and decreasing the hormone value decreases, the expression of p53 in this tumor. The no. of cells in the G1/G0 phase of the cell cycle was significantly higher, and the no. of cells in the G2/M phase was significantly lower in tumors grown in estradiol-treated mice than in tumors obtained from the non-treated group. Changes in p53 expression may possibly be explained by either altered transcription activity of the gene or increased half-life of the protein. Our results suggest an important role of estradiol in the progression of estrogen receptor (ER) pos. human endometrial adenocarcinomas.

Answer 36:

Bibliographic Information

Potentiation of antitumor activity of mitomycin C by estradiol: Studies of human breast carcinoma xenografts serially transplanted into nude mice. Oka, Shoichi; Kubota, Tetsuro; Takeuchi, Tooru; Kitajima, Masaki. School Medicine, Keio University, Tokyo, Japan. Journal of Surgical Oncology (1996), 61(4), 256-261. Publisher: Wiley-Liss, CODEN: JSONAU ISSN: 0022-4790. Journal written in English. CAN 125:1678 AN 1996:308211 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of exptl. cancer chemotherapy with mitomycin C (MMC) was studied using three estrogen-receptor (ER)-pos. (MCF-7, R-27, and Br-10) and one ER-neg. (MX-1) human breast carcinoma xenograft serially transplanted into nude mice, and the effect of estradiol (E2) priming on the antitumor activity of MMC was investigated. I.m. injection of E2 at 1 mg/kg changed the ER state and increased the growth fraction detected by flow cytometry, although the growth rate of ER-pos. tumors was not effective by E2 priming. MMC

suppressed the growth of the four xenografts in a dose-dependent manner. When 1 mg/kg E2 was administered 1 h before MMC treatment, which was given i.p. at a dose of 3 mg/kg, the antitumor activity of MMC was increased in comparison with MMC alone in ER-pos. strains, although the effect of MMC on MX-1 was not changed by E2-priming. Priming with E2 at this dose increases the growth fractions of ER-pos. breast carcinoma cells, which are sensitive to MMC, resulting in increased antitumor activity of MMC. This E2-primed MMC chemotherapy may be of value in the treatment of ER-pos. human breast cancer.

Answer 37:

Bibliographic Information

Radioimaging of human breast carcinoma xenografts in mice by [123I]-labeled Z-17α-iodovinyl-11β-chloromethyl-estradiol. Zeicher, M.; Delcorde, A.; Quivy, J.; Dupuis, Y.; Vervist, A.; Fruhling, J. DEPARTEMENT DE BIOLOGIE MOLECULAIRE, UNIVERSITE LIBRE DE BRUXELLES, Rhode-Saint-Genese, Belg. Nuclear Medicine and Biology (1996), 23(1), 69-73. Publisher: Elsevier, CODEN: NMBIEO ISSN: 0883-2897. Journal written in English. CAN 124:254709 AN 1996:166625 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Z-17α-iodovinyl-11β-chloromethylestradiol (Z-CMIV), a new selective estradiol deriv., can easily be labeled with high efficiency by radioactive iodine isotopes. Biodistribution studies and quant. scintigraphic imaging of human breast carcinoma xenografts in mice demonstrated continuous and selective accumulation of the [123I]Z-CMIV, in estrogen receptor (ER)-pos. target tumors, with significantly high target/nontarget ratio up to 48 h postinjection. A receptor-mediated mechanism of concn. of Z-CMIV in target tissues was confirmed by scintigraphic imaging and by biodistribution studies.

Answer 38:

Bibliographic Information

Estrogen stimulation and tamoxifen inhibition of leiomyoma cell growth in vitro and in vivo. Howe, Susan R.; Gottardis, Marco M.; Everitt, Jeffrey I.; Walker, Cheryl. Dep. Carcinogenesis, Univ. Texas, Smithville, TX, USA. Endocrinology (1995), 136(11), 4996-5003. Publisher: Endocrine Society, CODEN: ENDOAO ISSN: 0013-7227. Journal written in English. CAN 123:306819 AN 1995:897650 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Uterine leiomyomas (fibroids) are the most common gynecol. neoplasms and may be assocd. with significant morbidity. Recently, we described a rat model (Eker rat) of fibroid development in which reproductive tract leiomyomas develop spontaneously with high frequency. The present studies describe the estrogen and antiestrogen responsiveness of an Eker rat leiomyoma-derived cell line in vitro and a nude mouse xenograft system in vivo. In this cell line, estradiol stimulated growth in estrogen-depleted medium, whereas the nonsteroidal antiestrogen tamoxifen maximally inhibited cell proliferation in medium contg. 10% charcoal-stripped serum. Proliferation was also decreased by the biol. active tamoxifen metabolite 4-hydroxytamoxifen; the metabolite was more effective than the parent compd. in exerting this growth inhibition. Compared to placebo-treated controls, estradiol increased the size of tumors that developed in a nude mouse xenograft system, whereas tamoxifen increased tumor latency and decreased tumor size. This study of leiomyoma cells in a well defined system suggests that antiestrogens may prove efficacious in the treatment of this clin. important neoplasm.

Answer 39:

Bibliographic Information

Growth regulation by estradiol, progesterone and recombinant human epidermal growth factor of human breast carcinoma

xenografts grown serially in nude mice. Kubota, Tetsuro; Josui, Kazuya; Fukutomi, Takashi; Kitajima, Masaki. School Medicine, Keio University, Tokyo, Japan. Anticancer Research (1995), 15(4), 1275-8. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 124:46450 AN 1995:865993 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Four human breast carcinoma xenografts, MCF-7, Br-10, T-61 and MX-1, were transplanted into female nude mice with or without pretreatment with estradiol and progesterone. Hormone receptors including cytosol and nuclear estrogen receptor (ERc and ERn) and progesterone receptor (PgR) were assessed by the dextran-coated charcoal method and exchange assay; epidermal growth factor receptor (EGFR) was measured by the 1251-EGF binding assay. MCF-7 and T-61 were ERc-, ERn- and PgR- pos., but Br-10 was pos. only for ERc; MX-1 was neg. for these hormone receptors, but was the only xenograft showing EGFR. The growth of MCF-7 and Br-10 was enhanced by exogenous estradiol and progesterone, whereas the growth of T-61 was markedly inhibited by exogenous estradiol; the growth of MX-1 was not influenced by these sex steroids. Recombinant human epidermal growth factor (rhEGF) inhibited the growth of EGFR-pos. MX-1 dose-dependently, whereas no changes were obsd. in the growth of EGFR-neg. MCF-7, Br-10 and T-61 after treatment with rhEGF. This paradoxical inhibition of rhEGF on EGFR-pos. MX-1 might be due to down-regulation of EGFR, as shown in the ER-pos. xenograft T-61, whose growth was inhibited by estradiol.

Answer 40:

Bibliographic Information

Protein expression of p53 and Rb suppressor genes during the first passages of human endometrial adenocarcinomas heterotransplanted into nude mice. Horvath, Gyoergy; Leser, Gunilla; Delle, Ulla. Division Gynaecological Oncology, University Hospital, Goeteborg, Swed. In Vivo (1995), 9(1), 41-8. CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 123:53277 AN 1995:612153 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Five human endometrial adenocarcinomas were heterotransplanted into nude mice to study changes in p53 and Rb protein expression and loss of heterozygosity of these genes during the first nude mice passages. Three of five heterotransplanted tumors were established and measured. In one tumor overexpression of p53 protein was found in passage 1 and subsequently, whereas the original tumor did not over-express the protein. We concluded that the heterotransplantation, i.e. the new host environment, may lead to mutations in the p53 gene. Two tumors from patients and also during nude mice passages expressed p53 protein in two bands, which were probably the result of allele polymorphism. Both p53 and Rb protein expression were increased after growth in estradiol-treated animals. Our results suggest that several changes in the function of these suppressor genes, including mutations, occur during the first passages in nude mice. Consequently, the growth regulation of established tumors may differ from that in their original counterparts in the patients.

Answer 41:

Bibliographic Information

Hormonal regulation of proliferation and transforming growth factors gene expression in human endometrial adenocarcinoma xenografts. Gong, Yuewen; Murphy, Leigh C.; Murphy, Liam J. Faculty of Medicine, University of Manitoba, Winnipeg, MB, Can. Journal of Steroid Biochemistry and Molecular Biology (1994), 50(1-2), 13-19. CODEN: JSBBEZ ISSN: 0960-0760. Journal written in English. CAN 121:126060 AN 1994:526060 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors have previously shown that estrogen and progestins regulate both cellular proliferation and transforming growth factor (TGF) expression in human endometrial adenocarcinoma cells in vitro. In the current study the authors examd. the regulation of TGF-α

and -β1 expression in endometrial adenocarcinoma xenografts. Four human endometrial adenocarcinoma cell lines were inoculated into female BALB/c nude mice. Administration of 17β-estradiol (E2) increased tumor size in intact mice inoculated with Ishikawa, HEC-50 and HEC-1B cells but inhibited growth of HEC-1A xenografts. 4-Hydroxy tamoxifen (OH-Tam) had similar effects to E2 in animals carrying Ishikawa and HEC-1A cell xenografts but had no significant effect on growth of HEC-50 or HEC-1B xenografts. In intact mice inoculated with OH-Tam pellets and Ishikawa cells, the tumors were larger and had lower levels of TGF-α mRNA than in untreated or E2 treated mice. In mice carrying Ishikawa, HEC-50 and HEC-1B cell xenografts none of the hormones or agents tested altered TGF-β1 mRNA levels. In contrast, both E2 and OH-Tam significantly increased xenografts TGF-β1 mRNA levels in HEC-1A xenografts as well as significantly reduced tumor size. Medroxyprogesterone acetate (MPA) had no effect on tumor size of Ishikawa, HEC-1A and HEC-1B cell xenografts but significantly increased the size of HEC-50 xenografts. MPA significantly reduced TGF-α expression in Ishikawa cell xenografts but had no effect in the other cell xenografts. MPA had no effect on TGF-β1 expression in any of the xenografts. These observations demonstrate a discordance between the hormonal effects on TGF expression and cellular proliferation and argue against a major role for the TGFs in regulation of human endometrial adenocarcinoma cell proliferation in vivo.

Answer 42:

Bibliographic Information

In vitro and in vivo characterization of BR96 sFv-PE40. A single-chain immunotoxin fusion protein that cures human breast carcinoma xenografts in athymic mice and rats. Siegall, Clay B.; Chace, Dana; Mixan, Bruce; Garrigues, Ursula; Wan, Helen; Paul, Leland; Wolff, Edith; Hellstrom, Ingegerd; Hellstrom, Karl Erik. Pharm. Res. Inst., Bristol-Myers Squibb, Seattle, WA, USA. Journal of Immunology (1994), 152(5), 2377-84. CODEN: JOIMA3 ISSN: 0022-1767. Journal written in English. CAN 121:26368 AN 1994:426368 CAPLUS

Abstract

BR96 sFv-PE40 is a single-chain immunotoxin fusion protein targeted to the Ley antigen, which is expressed in many different human carcinomas as well as in normal gastrointestinal epithelium of humans and certain animals, including athymic rats, but not mice. In vitro binding anal. detd. that BR96 sFv-PE40 was similar in affinity to BR96 Fab. BR96 sFv-PE40 internalized rapidly, similar to BR96 IgG. H3396 cells, derived from metastatic human breast carcinoma, were established as tumor xenografts in estradiol-supplemented athymic mice and rats. H3396 tumor xenografts established in athymic mice (≤350 mm3) and rats (≤100 mm3) completely regressed after i.v. administration of BR96 sFv-PE40, given as 0.625 mg/kg (1.975 mg/m2) every 4th day for a total of 5 doses (mice) or 0.25 mg/kg (1.475 mg/m2) every 4th day for a total of 4 doses (rats). The tumors remained regressed for the duration of the study (>85 days postimplant), which represents >10 doubling times, indicating that the animals were cured. There was no toxicity in rats receiving a curative dose of 0.25 mg/kg, although liver and lung toxicity could be detected at a 16-fold higher dose, 4 mg/kg or 23.6 mg/m2. It is concluded that BR96 sFv-PE40 can cure tumor xenografts at well tolerated doses and also in the presence of Ley expression in normal tissues.

Answer 43:

Bibliographic Information

Effect of estradiol on tumor growth, cell kinetics and p53 oncoprotein expression in human endometrial adenocarcinoma heterotransplanted into nude mice. Horvath, Gyorgy; Baldetorp, Bo; Fernoe, Maarten; Johansson, Maria; Nesland, Jan; Trope, Claes. Dep. Oncol., Univ. Hosp., Lund, Swed. In Vivo (1993), 7(5), 451-6. CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 120:28452 AN 1994:28452 CAPLUS

Abstract

The aim of this study was to examine cell kinetics, steroid receptor activation, and expression of the p53 suppressor gene product during estradiol influenced vs. non-estradiol influenced growth in a human endometrial adenocarcinoma grown in nude mice for one year. The results show that progression of the tumor growth phenotype is independent of estradiol conditions in which human adenocarcinomas are grown. Long-term growth in estradiol-poor conditions results in estradiol resistance of the cell cycle, probably

accompanied by overexpression of the p53 protein. Estradiol-rich conditions, however, may protect at least to some extent, the same tumor, which retains higher sensitivity of cell proliferation to estradiol and normal prodn. of the p53 protein despite progressive changes in growth regulation.

Answer 44:

Bibliographic Information

Normal human breast xenografts activate N-nitrosodimethylamine: identification of potential target cells for an environmental nitrosamine. Zaidi, S. N. H.; Laidlaw, I.; Howell, A.; Potten, C. S.; Cooper, D. P.; O'Connor, P. J. Dep. Carcinog., Paterson Inst. Cancer Res., Manchester, UK. British Journal of Cancer (1992), 66(1), 79-83. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 117:186472 AN 1992:586472 CAPLUS

Abstract

Normal human breast tissue maintained as xenografts in female Balb/c (nu/nu) athymic mice metabolizes N-nitrosodimethylamine (NDMA) to active intermediates that will react with DNA. Administration of NDMA to mice with slow-release implants of 17β-estradiol which provide human physiol. (luteal phase) circulating estrogen levels and increase cell proliferation in the xenograft leads to an apparent increase in the extent of reaction with DNA compared to controls without estrogen implants. In mice with estrogen implants, measurements of the amts. of the promutagenic lesion, O6-methyl-2'-deoxyguanosine, formed in DNA clearly indicated a dose related increase in the extent of reaction. Detection of O6-methyl-2'-deoxyguanosine using immunohistochem. procedures revealed that the nuclei of cells of the glandular epithelium, supportive tissue, and adipose tissue, in decreasing order of prevalence, were pos. stained for the presence of this DNA lesion. Epithelial cells, which are the putative target cells for carcinogenesis in the breast, are therefore prone to promutagenic damage as a result of exposure to an environmental nitrosamine.

Answer 45:

Bibliographic Information

Estradiol induced changes in tumor growth and steroid receptor content in a heterotransplanted human endometrial adenocarcinoma. Horvath, Gyoergy; Fernoe, Maarten; Baldetorp, Bo; Cameron, Robert; Ranstam, Jonas. Dep. Oncol., Univ. Hosp., Lund, Swed. In Vivo (1991), 5(4), 401-6. CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 116:121133 AN 1992:121133 CAPLUS

Abstract

In a human endometrial adenocarcinoma heterotransplanted into nude mice, growth under estradiol-poor conditions led to decreased steroid receptor content, development of a less differentiated tumor, and enhanced tumor growth. On the other hand, estradiol-rich conditions increased estrogen receptor activation, progesterone receptor induction, and tumor differentiation. Thus, the estradiol conditions under which a tumor grows may have crit. effect on the course of tumor development.

Answer 46:

Bibliographic Information

Estrogen- and androgen-responsive growth of human ovarian adenocarcinoma heterotransplanted into nude mice. Sawada, Masumi; Terada, Nobuyuki; Wada, Akira; Mori, Yoichi; Yamasaki, Masato; Saga, Tsuneo; Endo, Keigo. Dep. Obstet. Gynecol., Kure Natl. Hosp., Kure, Japan. International Journal of Cancer (1990), 45(2), 359-63. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 112:152047 AN 1990:152047 CAPLUS

Abstract

A new line of human serous cystadenocarcinoma of the ovary, designated OVA-5, has been established in athymic nude mice. A strong correlation was noted between tumor vol. and plasma CA125 levels in mice bearing OVA-5 tumor. Growth of the OVA-5 tumor in castrated male nude mice was accelerated by s.c. administration of estradiol and 5α-dihydrotestosterone but not by progesterone. Estradiol and 5α-dihydrotestosterone also accelerated the growth of the OVA-5 tumor heterotransplanted into sialoadenectomized castrated male nude mice. No remarkable change was obsd. in the histol. appearances of the tumors between control groups and hormone-treated groups. Receptor assays revealed that the OVA-5 tumor had both estrogen and androgen receptors. Growth of the OVA-5 tumor is thus responsive to estrogen and androgen.

Answer 47:

Bibliographic Information

Contrasting actions of estradiol on the growth of human gastric cancer xenografts in nude mice. Tokunaga, Akira; Onda, Masahiko; Kiyama, Teruo; Nishi, Keigo; Mizutani, Takashi; Yoshiyuki, Toshiro; Shimizu, Yasuhito; Matsukura, Norio; Tanaka, Noritake; Asano, Goro. 1st Dep. Surg., Nippon Med. Sch., Tokyo, Japan. Japanese Journal of Cancer Research (1989), 80(12), 1153-5. CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 112:92039 AN 1990:92039 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of estradiol on the growth of 6 human gastric cancer xenografts in nude mice showed a variety of responses, including 1 case of stimulation, 2 of inhibition, and 3 of no effect. Neither the histol. features of the original tumor nor the estrogen-binding capacity seemed to be related to the response to estradiol. Apparently, the growth of some human gastric cancers can be modulated by estradiol.

Answer 48:

Bibliographic Information

Effect of 17β-estradiol on the growth of estrogen receptor-positive human melanoma in vitro and in athymic mice. Feucht, Kenneth A.; Walker, Michael J.; Das Gupta, Tapas K.; Beattie, Craig W. Coll. Med., Univ. Illinois, Chicago, IL, USA. Cancer Research (1988), 48(24, Pt. 1), 7093-101. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 110:51455 AN 1989:51455 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Physicochem. properties of an estrogen-binding protein were characterized in 3 human melanoma cell lines, UISO-MEL-1, UISO-MEL-2, and UISO-MEL-4. Estrogen binding to melanoma cytosol was saturable, specific for estrogens, and represented by a single class of high-affinity, limited-capacity binding sites (dissocn. const. 5.5 × 10-10M, 2.7 fmol/mg of cytosol protein, UISO-MEL-2; 2.2 × 10-10M, 7.8, UISO-MEL-4); UISO-MEL-1 cytosols did not bind estradiol. The binding protein in UISO-MEL-2 and -4 sedimented at 8.5 S and 9.2 S, resp., in the presence of 10 mM Na molybdate. Solid-phase RIA with a monoclonal antibody specific for human estrogen receptor (H222 spλ) showed good correlation (r = 0.84) with a hydroxyapatite biochem. assay of identical melanoma cytosols. Exposure of UISO-MEL-2 to estradiol produced a time- and temp.-dependent increase in total nuclear receptor for estrogen in vitro. Estradiol treatment of athymic mice also increased cytosol progesterone receptor content in UISO-MEL-2 and UISO-MEL-4 xenografts. Estradiol had no effect on the plating efficiency or growth of any melanoma cell line or normal melanocytes in vitro. Tamoxifen also had no effect on melanoma growth in vitro. In contrast, chronic exposure of athymic mice carrying estrogen receptor-pos. UISO-MEL-2 to estradiol resulted in a sex-dependent increase in tumor latency and overall inhibition of tumor growth. Evidently, a subset of human melanomas contains limited amts. of an estrogen-binding protein similar to that obsd. in other estrogen-responsive tissues. The lack of effect of estradiol on melanocyte and melanoma growth in vitro, coupled with a decrease in tumor growth in athymic mice, suggests that whereas inhibition may be receptor mediated, possible indirect actions of estradiol must also be

considered.

Answer 49:

Bibliographic Information

Effects of estradiol on estrogen receptor, progesterone receptor, and tyrosinase in hamster melanoma transplanted into athymic mice. Hitselberger, M. Helen; Schleicher, Rosemary L.; Beattie, Craig W. Coll. Med., Univ. Illinois, Chicago, IL, USA. Cancer Research (1988), 48(13), 3720-7. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 109:67131 AN 1988:467131 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nuclear estrogen binding was characterized in HM-1, a malignant hamster melanoma cell line, transplanted into male and female athymic mice following acute, subchronic, and chronic injection of estradiol. Nuclear binding was saturable, of high affinity (1010 M-1) and readily sol. in low-salt buffer. Satn. analyses revealed that [3H]estradiol >5.0 nM apparently bound to a second class of lower-affinity (109 M-1), higher-capacity cytosol sites. Enzyme-linked immunoassay with a specific monoclonal antibody (H222 Spγ) directed against the human estrogen receptor protein was in excellent agreement with values obtained using hydroxyapatite to sep. bound from free ligand. Nuclear estrogen receptor content in HM-1 cells was increased maximally 1 h after acute s.c. injection of a low dose (0.1 μg) of estradiol. The increase in nuclear receptor content was accompanied by an apparent rapid redn. in cytosol binding. Subchronic (3 days) and chronic exposure (35 days) to estradiol also produced a significant, dose-related increase in tumor nuclear estrogen receptor content. Cytosol binding for progestin was low (≤2 fmol) to absent in HM-1 xenografts not exposed to estradiol. Subchronic and chronic exposure to estradiol induced a dose-related, specific, high-affinity (109 M-1) cytosol binding protein for progestin(s) in HM-1 xenografts carried in male and female athymic mice. In contrast, progestin binding to nuclear receptor was not increased in estrogen-primed animals, nor did acute injection of progesterone (100 μg s.c.) increase the amt. of saturable, high-affinity (109 M-1) nuclear progestin receptor in control or estradiol-primed athymic mice. In contrast to the induction of progestin binding, tyrosinase activity was not altered by a similar exposure to estradiol when assayed at a satg. concn. of tyrosine. Thus, the estrogen receptor in HM-1 cells may be functional, but pigmentary changes obsd.

in mammals following chronic exposure to estradiol may not be mediated by a direct effect on the rate-limiting enzyme of melanin synthesis.

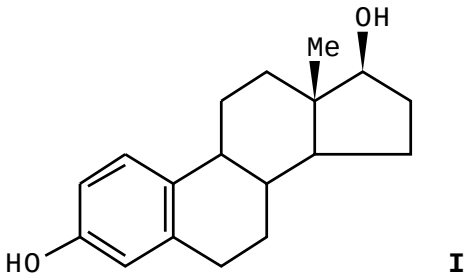
Answer 50:

Bibliographic Information

Experimental hormonal treatment of human ovarian carcinomas xenotransplanted in nude mice. Kleine, W.; Fuchs, A.; Niederstadt, T.; Teufel, G.; Pfleiderer, A. Universitaetsfrauenklin., Freiburg, Fed. Rep. Ger. Editor(s): Bastert, Gunther B.; Fortmeyer, Hans Peter; Schmidt-Matthiesen, Heinrich. Thymusaplastic Nude Mice Rats Clincial Oncol., Proc. Symp. (1981), Meeting Date 1979, 137-43. Publisher: Fischer, Stuttgart, Fed. Rep. Ger CODEN: 46XEAJ Conference written in English. CAN 96:97885 AN 1982:97885 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of medrogestone [977-79-7], gestonorone [2137-18-0], tamoxifen [10540-29-1], and estradiol (I) [50-28-2] were studied on xenotransplanted human ovarian carcinomas in nude mice and the effect correlated with the presence or absence of steroid receptors. Growth of transplanted tumor was independent of the sex of the recipient. Medrogestone increased the growth rate of transplanted tumor independently of the presence of steroid receptor. Tamoxifen and gestonorone produced variable results and had no effect, resp. I affected tumor growth in an estrogen receptor-dependent manner. In receptor pos. tumors, I decreased growth whereas in estrogen receptor neg. tumors it increased growth. Evidently, hormonal treatment is less effective than cytotoxic chemotherapy for ovarian carcinoma xenotransplanted to nude mice.



I

Answer 51:

Bibliographic Information

Genes regulated by estrogen in breast tumor cells in vitro are similarly regulated in vivo in tumor xenografts and human breast tumors. Creighton Chad J; Cordero Kevin E; Larios Jose M; Miller Rebecca S; Johnson Michael D; Chinnaiyan Arul M; Lippman Marc E; Rae James M Bioinformatics Program, University of Michigan Medical Center, Ann Arbor, MI 48109, USA Genome biology (2006), 7(4), R28. Journal code: 100960660. E-ISSN:1465-6914. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 16606439 AN 2006387240 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Estrogen plays a central role in breast cancer pathogenesis. Although many studies have characterized the estrogen regulation of genes using in vitro cell culture models by global mRNA expression profiling, it is not clear whether these genes are similarly regulated in vivo or how they might be coordinately expressed in primary human tumors. RESULTS: We generated DNA microarray-based gene expression profiles from three estrogen receptor alpha (ERalpha)-positive breast cancer cell lines stimulated by 17beta-estradiol (E2) in vitro over a time course, as well as from MCF-7 cells grown as xenografts in ovariectomized athymic nude mice with E2 supplementation and after its withdrawal. When the patterns of genes regulated by E2 in vitro were compared to those obtained from xenografts, we found a remarkable overlap (over 40%) of genes regulated by E2 in both contexts. These patterns were compared to those obtained from published clinical data sets. We show that, as a group, E2-regulated genes from our preclinical models were co-expressed with ERalpha in a panel of ERalpha+ breast tumor mRNA profiles, when corrections were made for patient age, as well as with progesterone receptor. Furthermore, the E2-regulated genes were significantly enriched for transcriptional targets of the myc oncogene and were found to be coordinately expressed with Myc in human tumors. CONCLUSION: Our results provide significant validation of a widely used in vitro model of estrogen signaling as being pathologically relevant to breast cancers in vivo.

Answer 52:

Bibliographic Information

The decreased influence of overall treatment time on the response of human breast tumor xenografts following prolongation of the potential doubling time (Tpot). Sarkaria J N; Fowler J F; Lindstrom M J; Jordan V C; Mulcahy R T Department of Human Oncology, University of Wisconsin-Madison School of Medicine International journal of radiation oncology, biology, physics (1995), 31(4), 833-40. Journal code: 7603616. ISSN:0360-3016. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 7860396 AN 95164297 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

PURPOSE: Repopulation during fractionated radiotherapy has been postulated to result in a significant loss in local control in rapidly proliferating tumors. Clinical data suggest that accelerated fractionation schedules can overcome the influence of repopulation by limiting the overall treatment time. Unfortunately, accelerated therapy frequently leads to increased acute reactions, which may become dose limiting. An alternative to accelerated fractionation would be to decrease the rate of repopulation during therapy. To test the potential efficacy of this alternative, we examined the effect of reducing tumor proliferation rate on the response of MCF-7 human breast carcinoma xenografts treated with a short vs. a long course of fractionated therapy. To reduce the proliferation rate, we deprived nude mice transplanted with MCF-7 xenografts of the growth-stimulating hormone estradiol (E2). We have previously reported that E2 deprivation increases the potential doubling time (Tpot) for MCF-7 xenografts from a mean of 2.6 days to 5.3 days ($p < 0.001$). METHODS AND MATERIALS: E2-stimulated and E2-deprived MCF-7 breast carcinoma xenografts were clamped hypoxically and irradiated with four fractions of 5 Gy each, using either a short (3-day) or long (9-day) treatment course. E2 stimulation was restored in all animals at the completion of irradiation. Radiation response was determined by regrowth time and regrowth delay of the irradiated tumors as compared to unirradiated controls. RESULTS: Prolongation of therapy in rapidly proliferating, E2-stimulated tumors (Tpot approximately 2.6 days) resulted in a significant decrease in regrowth time in two identical experiments. With results pooled for analysis, the regrowth times for the short and long treatments were 62 and 32 days, respectively (combined $p < 0.001$). The shorter regrowth times suggest that there was less overall tumor damage with the longer fractionated radiotherapy course.

No significant difference in regrowth time was observed in the more slowly proliferating, E2-deprived tumors (Tpot approximately 5.3 days) treated with either the short or long regimen. Median regrowth times were 48 and 54.5 days for the short and long treatments, respectively (combined $p = 0.14$). Similar changes were observed in regrowth delay. CONCLUSIONS: Reduction in the rate of cell proliferation, induced by E2 deprivation in MCF-7 human breast xenografts during fractionated radiotherapy, resulted in a significantly decreased dependence on overall treatment time in comparison to the more rapidly proliferating E2-stimulated tumors. This model suggests that pharmacologically induced reduction in the rate of tumor cell proliferation during a course of fractionated radiotherapy may be a viable alternative to accelerated fractionation for the treatment of rapidly proliferating tumors.

Answer 53:

Bibliographic Information

Establishment and characterization of human ovarian endometrioid carcinoma cell line. Fujii T Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine Nippon Sanka Fujinka Gakkai zasshi (1989), 41(2), 161-6. Journal code: 7505749. ISSN:0300-9165. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2723484 AN 89256920 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

A new cell line, designated as HOC-I, was established from a recurrent region of ovarian endometrioid carcinoma. HOC-I was subcultivated more than 55 times. 1) The monolayer culture cells showed a pavement like arrangement with polygonal cells and had a tendency to pile up. PAS positive substance could be seen in the cytoplasm. Desmosomes, microvilli and well developed cell organelles could be found by electron microscopy. 2) The population doubling time was about 75 hours. The chromosomal number showed pseudodiploidy of which the mode was 46. 3) By heterotransplantation to the nude athymic mouse, the tumor easily developed. 4) The effects of estradiol and progesterone on the cellular growth were assessed by the 3H-TdR uptake test. Estradiol increased 3H-TdR uptake of HOC-I but progesterone decreased it. These data suggested that HOC-I had sex-steroid hormone dependency. 5) Estrogen receptor was not detected in HOC-I by the ER-EIA method or the ER-ICA method. 6) The HOC-I cells produced CA125 and TPA in culture media.

Answer 54:

Bibliographic Information

Lymphoscintigraphy of human colorectal carcinoma metastases in athymic mice by use of radioiodinated B72.3

monoclonal antibody. Shah S A; Gallagher B M; Sands H Journal of the National Cancer Institute (1987), 78(6), 1069-77. Journal code: 7503089. ISSN:0027-8874. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 3473248 AN 87226969 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The potential of radioiodinated monoclonal antibody B72.3 for lymphoscintigraphy was evaluated, using suitable animal models of a human colorectal carcinoma. LS174T xenografts were grown at various sites in beta-estradiol-pretreated athymic mice, and the development of metastases in different organs was assessed histologically. After iv inoculation of the mice, 66% of the animals developed "metastases" to the axillary lymph nodes. Of these mice, 100% also developed multiple tumors on their backs and 79% had lung micrometastases. Livers, kidneys, and spleens showed no evidence of tumor growth. In 33% of the mice in which primary LS174T tumors had been removed from the hindfoot pad, metastases to the popliteal lymph nodes were observed 3 1/2 weeks after tumor implantation. BALB/c (nu/nu) female mice bearing axillary and popliteal lymph node metastases were used to test the potential of radiolabeled B72.3 antibody (an IgG1) as a lymphoscintigraphic agent. A monoclonal antibody against horseradish peroxidase (also an IgG1), which did not bind LS174T tumor cells in vitro, served as a control. Both normal and tumor-bearing axillary and popliteal lymph nodes imaged up to 6 hours after the sc injection of 20-40 mu Ci of 125I-labeled B72.3 into either the forefoot or hindfoot pads. The localization index (L.I.) (specific/nonspecific antibody in tumor divided by specific/nonspecific antibody in blood) for LS174T tumors in lymph nodes was approximately 1 during the first 6 hours after antibody injection, thus indicating no specific antibody accumulation. Twenty-four hours and later after sc injection, images of nodal metastases (14-477 mg) and specific antibody accumulations were observed. At these times the L.I.'s ranged 1.5-3.5. Tumor-negative nodes did not image at 24 hours after injection of 125I-labeled B72.3. The L.I.'s of the normal nodes and of other tissues from these mice were about 1.0 at 24 hours, indicating no specific antibody accumulation.

Autoradiographic analysis of lymph nodes containing LS174T tumor showed heterogeneous antibody distribution of B72.3 within tumor sections with heavy patches of antibody accumulation in mucin globules. In lymph nodes the normal lymphocytes adjacent to the LS174T tumor cells showed no antibody accumulation. The lack of specific, early antibody accumulation by LS174T tumor-bearing nodes in mice suggests that B72.3 does not accumulate in nodal metastases to the degree necessary to consider it a potential agent for use in lymphoscintigraphy.

Answer 55:

Bibliographic Information

Antitumor activity and pharmacokinetics of estra-1,3,5 (10)-triene-3,17 beta-diol, 3-benzoate, 17-((4-(4-bis(2-chloroethyl)amino)phenyl)-1-oxobutoxy) acetate) (Bestrabucil) in human tumor xenografts serially transplanted into nude mice. Kubota T; Kawamura E; Suzuki T; Yamada T; Toyoda H; Miyagawa T; Kurokawa T Japanese journal of clinical oncology (1986), 16(4), 357-64. Journal code: 0313225. ISSN:0368-2811. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3795532 AN 87087277 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Bestrabucil (KM2210), the benzoate of an estradiol-chlorambucil conjugate, was used experimental cancer chemotherapy against 13 human tumor xenografts serially transplanted into nude mice, and its pharmacokinetics was studied. The tumors were one esophageal, two gastric, six colon, one cholecystic and three breast carcinomas. Two tumor tissue fragments approximately 3 X 3 X 3 mm were inoculated into BALB/cA nude mice, which were then treated with KM2210 at doses of 100, 200 and 300 mg/kg/day orally starting 24 hr after the transplantation or when the tumor reached a weight of 100-300 mg. The concentration of KM2210 and its derivatives in the tumor xenografts, normal muscular tissue and blood were assayed by high performance liquid chromatography. Six out of 13 xenografts were found to be sensitive to KM2210. The concentrations of KM2210 and its derivatives in the tumor tissues of the sensitive xenografts were five to 10 times higher than those in blood and muscular tissue, and the antitumor activity correlated well with the area under the curve of active metabolites of KM2210 in the tumor.

Answer 56:

Bibliographic Information

Establishment and characterization of human ovarian endometrioid carcinoma cell line. Uehara S; Soh K; Hoshiai H; Yajima A; Suzuki M; Abe H Nippon Sanka Fujinka Gakkai zasshi (1983), 35(1), 19-26. Journal code: 7505749. ISSN:0300-9165. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 6827161 AN 83137370 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Ascitic fluid was obtained from the patient of ovarian endometrioid cancer. Collected cells were incubated with Eagle's MEM containing 15% fetal calf serum at 37 degrees C under humidified 5% CO2 and 95% air. The epithelial colonies grew rapidly and were released without fibroblast cells. After the first passage, the cells are growing without interruption for over one year and 35 transfer generations. This cell line has following charactors: 1) The monolayer cultured cells appeared epithelial, pavement like arrangement and piling up, without contact inhibition. 2) In the cytoplasma PAS positive substance can be seen. 3) Desmosome-like structure, gap junction, microvilli and well developed cell organelles can be found by electron microscopy. 4) Chromosomal number shows pseudodiploidy which mode is 47. A submetacentric chromosome was present in all karyotype and identified by G-banding. It consists of No. 11 and a part of No. 1. 5) By heterotransplantation to the nude athymic mouse, the tumor easily develops. 6) By estradiol and promegestone its growth was inhibited. 7) Estrogen and progesterone receptors were not detected in the cytosol.